Update on SARS-CoV-2 Vaccines: Trust the Process?

Sean O’Leary, MD, MPH, FAAP
December 4, 2020
Financial Disclosure

I have no relevant financial relationships with any commercial interests
Late Breaker: An evolving outbreak of a 2019 novel coronavirus (2019-nCoV) that began in Wuhan City, Hubei Province, China now includes over 300 reported cases, including in health care workers. Current data suggest the virus is of zoonotic origin, but there has been confirmed human-to-human transmission. Additional cases have been identified in Taiwan, South Korea, Japan, Thailand, and the United States (first case identified in an adult male on 1/21/20 in Washington state who had traveled from Wuhan). Patients who present with fever and symptoms of lower respiratory illness should be screened for a travel history to Wuhan City in the previous 14 days and reported to CDPHE. This is an evolving situation - for more information please see the CDC website:
COVID-19 in Colorado: Not Looking Good

Cases of COVID-19 in Colorado by Date Reported to the State

Patients Currently Hospitalized for COVID-19
Respiratory Pathogens Detected in the Last 8 Weeks

Adenovirus
Atypical Bacteria
Coronavirus
COVID-19
HMPV
Influenza A
Influenza B
Parafiu
Rhino/Entero
RSV

Positive Specimen Count

10/4/20
10/11/20
10/18/20
10/25/20
11/1/20
11/8/20
11/15/20
11/22/20
### Racial & Ethnic Disparities in COVID-19, US

<table>
<thead>
<tr>
<th>Rate ratios compared to White, Non-Hispanic Persons</th>
<th>American Indian or Alaska Native, Non-Hispanic persons</th>
<th>Asian, Non-Hispanic persons</th>
<th>Black or African American, Non-Hispanic persons</th>
<th>Hispanic or Latino persons</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASES¹</td>
<td>2.8x higher</td>
<td>1.1x higher</td>
<td>2.6x higher</td>
<td>2.8x higher</td>
</tr>
<tr>
<td>HOSPITALIZATION²</td>
<td>5.3x higher</td>
<td>1.3x higher</td>
<td>4.7x higher</td>
<td>4.6x higher</td>
</tr>
<tr>
<td>DEATH³</td>
<td>1.4x higher</td>
<td>No Increase</td>
<td>2.1x higher</td>
<td>1.1x higher</td>
</tr>
</tbody>
</table>

Race and ethnicity are risk markers for other underlying conditions that impact health — including socioeconomic status, access to health care, and increased exposure to the virus due to occupation (e.g., frontline, essential, and critical infrastructure workers).

“In Denver, Colorado, the majority of adult COVID-19 cases (55%), hospitalizations (62%), and deaths (51%) were among Hispanic adults, double the proportion of Hispanic adults in Denver (24.9%).”
Vaccine Confidence & Communication

- **Strong science** is a necessary starting point
- Healthcare professional **confidence** in and commitment to vaccines is a necessary starting point
- **Trust** in the process is paramount
Vaccine Confidence & Communication

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Strong science is a necessary starting point
Healthcare professional confidence in and commitment to vaccines is a necessary starting point
Trust in the process is paramount

You can stop the spread of misinformation by looking for facts instead of rumors
Strong science is a necessary starting point.

Healthcare professional confidence in and commitment to vaccines is a necessary starting point.

Trust in the process is paramount.
Objectives

By the end of this presentation, audience members should be able to:

• Describe the current COVID-19 vaccine candidates and their mechanisms of action
• Explain the process of licensure and approval
• Describe the safety monitoring systems that are in place to ensure safety of COVID-19 vaccines
• Understand the reasoning behind the current plans for allocation of COVID-19 vaccines
Outline

- Vaccine Candidates
- Immunology of Vaccination and Mechanisms of Action
- Vaccine Licensing and Recommendation
- Post-licensure Safety Monitoring
- Vaccine Allocation and Implementation
### Coronavirus Vaccine Tracker

By Carl Zimmer, Jonathan Corum and Sul-Lee Wee  
Updated December 2, 2020

<table>
<thead>
<tr>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
<th>LIMITED</th>
<th>APPROVED</th>
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<tr>
<td>41</td>
<td>17</td>
<td>13</td>
<td>7</td>
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</tbody>
</table>

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

### VACCINE CANDIDATES
Operation Warp Speed Vaccines

mRNA
- Moderna
- Pfizer/BioNTech

Adenoviral vector
- AstraZeneca
- Janssen

Recombinant protein
- Novavax
- GSK Sanofi
General Summary of Trials So Far for OWS Candidates

- Immunogenicity profiles all look favorable with robust antibody responses to the spike protein of SARS-CoV-2 and Th1-biased CD4+ T-cell responses
  - Th1-biased is what we want (Th2-bias more prone to allergic phenomenon)
- Safety profiles so far also look generally favorable
- For the phase 3 trials, the companies have been mostly successful at enrolling diverse populations, in terms of race/ethnicity, age, and comorbid conditions
94.1% efficacy
196 cases of COVID, 185 in placebo group, 11 in vaccine group
30 severe cases, all in placebo group
196 cases included 33 older adults (>65), 42 identified from “diverse communities”
No significant safety concerns
Up to 20 million doses by end of 2020, 500 million to a billion in 2021
• Committed 100 million doses to US
Modern Announces Primary Efficacy Analysis in Phase 3 COVE Study for Its COVID-19 Vaccine Candidate and Filing Today with U.S. FDA for Emergency Use Authorization

November 30, 2020 at 6:59 AM EST

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• Committed 100 million doses to US
• December 2: Registered for trial for ages 12-17; 3000 participants

moderna

Modern Plans to Begin Testing Its Coronavirus Vaccine in Children

The company said the trial would involve children ages 12 through 17.

mRNA
PFIZER AND BIONTECH CONCLUDE PHASE 3 STUDY OF COVID-19 VACCINE CANDIDATE, MEETING ALL PRIMARY EFFICACY ENDPOINTS

Wednesday, November 18, 2020 - 06:59am

- EUA submitted 11/20
- 95% effective against COVID-19 beginning 28 days after the first dose
- 170 confirmed cases of COVID-19 were evaluated, 162 in placebo group versus 8 in vaccine group
- Efficacy was consistent across age, gender, race and ethnicity demographics
- Observed efficacy in adults over 65 years of age was over 94%
- Safety data milestone required by FDA for Emergency Use Authorization (EUA) has been achieved, and no major safety concerns
- Submitted safety data on 100 children 12-15 years of age in EUA
- The companies expect to produce globally up to 50 million vaccine doses in 2020 and up to 1.3 billion doses by the end of 2021
  - Committed to 100 million doses to US, probably 20 million by end of the 2020
AZD1222 vaccine met primary efficacy endpoint in preventing COVID-19

Two different dosing regimens demonstrated efficacy with one showing a better profile

No hospitalisations or severe cases of COVID-19 in participants treated with AZD1222

- Half-dose followed by full-dose (n=2,741) efficacy 90%
- Full-dose/full-dose (n=8,895) efficacy 62%
- Reduced number of asymptomatic cases
- No serious safety events reported
- In separate trial, immunogenicity in older adults similar to younger
- 300 million doses slated for US; manufacturing capacity 2 billion doses/year

US: 4 million doses by end of 2020, 40 million first quarter of 2021
Storage Requirements, Ordering and other Details

- **Pfizer:** -70°C up to 6 months
  - Specialty shippers can be refreshed with dry ice every 5 days for up to 15 days
  - Once thawed, can be refrigerated for 5 days
  - Minimum order is 975 doses

- **Moderna:** -20°C up to 6 months
  - Can last in refrigerator up to 30 days, room temperature up to 12 hours
  - Minimum order is 100 doses

- **AstraZeneca, Janssen, Novavax, Sanofi/GSK** all 2-8°C
IMMUNOLOGY OF VACCINATION AND MECHANISMS OF ACTION
Overview of Immune Responses

Immunity

Adaptive Immunity

Natural

Passive (maternal)

Active (infection)

Artificial

Passive (antibody transfer)

Active (immunization)

Innate Immunity

Slide courtesy of Paul Goepfert, UAB
Collaboration of Innate and Adaptive Immune Responses

Innate Immunity

- Inbuilt immunity to resist infection
- Present from birth
- Not enhanced by second exposure; has no memory
- Examples include neutrophils, monocytes, dendritic cells, natural killer (NK) cells
- Is poorly effective without adaptive immunity, BUT
- Essential for an optimal adaptive immune response

Adaptive Immunity

- Learned by experience
- Confers pathogen-specific immunity
- Enhanced by second exposure
- Has memory
- Uses cellular and humoral (antibodies) components
- Is poorly effective without innate immunity

Slide courtesy of Paul Goepfert, UAB
Lymphocyte Subsets

T CELLS

CLP
Common lymphoid precursor

B CELLS

T

CLP

Th
CD4 T
Activate B cells and macrophages
T HELPER CELL or CD4 T cells

CTL
CD8 T
Kill virus-infected cells
CYTOTOXIC T LYMPHOCYTES or CD8 T cells

PC
Produce antibodies
PLASMA CELLS
Collaboration of Innate and Adaptive Responses
COVID Immunology 101
**Imune response**

Specialized ‘antigen presenting cells’ (APCs) engulf the virus and display portions of it to activate T-helper cells.

T-helper cells enable other immune responses:
- B cells make antibodies that can block the virus from infecting cells, as well as mark the virus for destruction.
- Cytotoxic T cells identify and destroy virus-infected cells.

- **B cell**
  - Produces anti-coronavirus antibody
  - Prevents virus from binding, or tags it for destruction

- **Cytotoxic T cell**
  - Destroys infected cells

Long-lived ‘memory’ B and T cells that recognize the virus can patrol the body for months or years, providing immunity

*Simplified

Graphics: Nik Spencer/Nature
Corona = crown or circle of light

SARS-CoV-2 Spike Protein: Viral Entry

Viral-vector vaccines

- Potential for strong immune response
- May or may not need booster doses
- Example: Ebola vaccine
  - replicating; OWS candidates non-replicating
- AstraZeneca/Oxford
  - Enrolling in Colorado
- Janssen (Johnson and Johnson)
  - Results of phase 3 expected by end of 2021 (testing both 1 and 2 doses)
  - University of Colorado currently enrolling
Protein Subunit Vaccines

• Likely to require adjuvants
• Likely to require multiple doses
• Example: acellular pertussis vaccines
• OWS Candidates:
  • Novavax: Phase 3 in UK enrolling, Phase 3 in US just starting
    • Could deliver 100 million doses to US first quarter 2021
  • GSK/Sanofi (same design as Flublok): Phase 3 starting 12/2020, results expected mid-2021
    • Will be enrolling at University of Colorado
Virus-like Particle Vaccines

- Empty virus shell
- Strong immune response
- Can be difficult to manufacture
- Examples: HPV and hepatitis B vaccines
- Lots of candidates, but only one phase 1, most pre-clinical
mRNA Vaccines

At least 20 teams are aiming to use genetic instructions (in the form of DNA or RNA) for a coronavirus protein that prompts an immune response. The nucleic acid is inserted into human cells, which then churn out copies of the virus protein; most of these vaccines encode the virus’s spike protein.

RNA- and DNA-based vaccines are safe and easy to develop: to produce them involves making genetic material only, not the virus. But they are unproven: no licensed vaccines use this technology.
Collaboration of Innate and Adaptive Responses

- T helper cell
- CD4^+ cells
- B cells
- Antibodies
- APC
- MHC2
- Antigen
- Killer T cells
- Macrophages
Collaboration of Innate and Adaptive Responses

Measles vaccine

- APC
- MHC2
- CD4+
- T helper cell
- B cells
- Antibodies
- Macrophages
- Killer T cells
Collaboration of Innate and Adaptive Responses

Measles vaccine
Weakened virus
A virus is conventionally weakened for a vaccine by being passed through animal or human cells until it picks up mutations that make it less able to cause disease. Codagenix in Farmingdale, New York, is working with the Serum Institute of India, a vaccine manufacturer in Pune, to weaken SARS-CoV-2 by altering its genetic code so that viral proteins are produced less efficiently.

Inactivated virus
In these vaccines, the virus is rendered uninfectious using chemicals, such as formaldehyde, or heat. Making them, however, requires starting with large quantities of infectious virus.

Vaccine

or

Antigen-presenting cell
Coronavirus peptide

Cell

Virus replicates

Immune response
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![Diagram of vaccine interaction]
NUCLEIC-ACID VACCINES

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RNA- and DNA-based vaccines are safe and easy to develop: to produce them involves making genetic material only, not the virus. But they are unproven: no licensed vaccines use this technology.
RNA vaccine

RNA is often encased in a lipid coat so it can enter cells
SARS-CoV-2 Spike Protein: Viral Entry

Corona = crown or circle of light

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mRNA vaccines give the immune system genetic instructions to recognise the virus.

**How the Pfizer-BioNTech vaccine works**

1. **Spike** protein
2. mRNA lipid nanoparticle
3. Cell

**Scientists focus on the genetic sequence for the virus’s ‘spike’ protein. This is used to synthesise an mRNA sequence – instructions that cells can use to make the ‘spike’ protein.**

**The synthetic mRNA is packaged in a lipid nanoparticle that delivers the instructions to a cell.**

**Once inside the cell, its cellular machinery follows the mRNA instructions to produce the viral protein. This is displayed on the surface of the cell and stimulates an immune system response.**

Source: Pfizer

FINANCIAL TIMES
mRNA vaccines give the immune system genetic instructions to recognise the virus

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Source: Pfizer
Vaccine Safety: But What about the...

The mRNA in the vaccines breaks down in a matter of hours...
VACCINE LICENSING AND RECOMMENDATION
Path from clinical development to recommendation

Clinical Development
- Generates safety, immunogenicity, and efficacy data
- Close coordination within OWS (DHHS [CDC, NIH, ASPR], DoD)
- Manufacturing of vaccine - could save months of time post-approval

FDA
- Licensure
- Emergency Use Authorization (AVA Anthrax for PEP)
- Expanded Access IND (MenB vaccine during college outbreaks)

ACIP
- Review Evidence, utilize Evidence to Recommendation Framework
- Make recommendations regarding the use of vaccines to the CDC Director

CDC Recommendation
Post-approval monitoring
Vaccine Development: Traditional versus SARS-CoV-2
Vaccine Licensing Process: Safety First

How a new vaccine is developed, approved and manufactured

The Food and Drug Administration (FDA) sets rules for the three phases of clinical trials to ensure the safety of the volunteers. Researchers test vaccines with adults first.

PHASE 1

20-100 healthy volunteers

- Is this vaccine safe?
- Does this vaccine seem to work?
- Are there any serious side effects?
- How is the size of the dose related to side effects?

PHASE 2

several hundred volunteers

- What are the most common short-term side effects?
- How are the volunteers' immune systems responding to the vaccine?

PHASE 3

hundreds or thousands of volunteers

- How do people who get the vaccine and people who do not get the vaccine compare?
- Is the vaccine safe?
- Is the vaccine effective?
- What are the most common side effects?

FDA licenses the vaccine only if:

- It's safe and effective
- Benefits outweigh risks

Vaccines are made in batches called lots.

Manufacturers must test all lots to make sure they are safe, pure and potent. The lots can only be released once FDA reviews their safety and quality.

The FDA inspects manufacturing facilities regularly to ensure quality and safety.

For more information, visit https://www.fda.gov/cber

*www.cdc.gov/vaccines/parents/infographics/journey-of-child-vaccine.html From: Frank DeStefano, CDC presentation, 30-31 May 2019
FDA Compared to ACIP

- FDA licenses vaccines and ACIP makes recommendations for vaccine use
- FDA is a regulatory agency while ACIP has no regulatory authority
- FDA does not regulate the practice of medicine
- FDA licenses a vaccine based only on results of clinical studies and other data submitted by a vaccine manufacturer
- ACIP recommendations may differ from FDA licensure

Development of vaccine recommendations and policies

What is VRBPAC and why should I trust them?

• 15 voting members, primarily experts in vaccines, infectious diseases, and public health
• Almost all non-governmental (no political appointees)
• Lots of pediatric representation
What is VRBPAC and why should I trust them?

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- Lots of pediatric representation

Paul Spearman, M.D.
Expertise: Pediatric & Infectious Diseases
Term: 05/9/2018-01/31/2022
Director, Division of Infectious Diseases
Albert B. Sabin Chair in Pediatric Infectious Diseases
Cincinnati Children's Hospital Medical Center
Professor, Department of Pediatrics
University of Cincinnati School of Medicine
Cincinnati, OH 45229

Paul Offit, M.D.
Expertise: Infectious Diseases
Term: 02/01/2018-01/31/2022
Professor of Pediatrics
Division of Infectious Diseases
Abramson Research Building
The Children's Hospital of Philadelphia
Philadelphia, PA 19104

Amanda Cohn
Expertise: Pediatrics, Vaccines
Term: 02/01/2020-01/31/2024
Chief Medical Officer
National Center for Immunizations and Respiratory Diseases
Centers for Disease Control and Prevention
Atlanta, GA 30333

Hayley Altman-Gans, M.D.
Expertise: Pediatrics, Infectious Diseases
Term: 06/21/2019-01/31/2023
Professor
Department of Pediatrics
Stanford University Medical Center
Stanford, CA 94305

H. Cody Meissner, M.D.
Expertise: Infectious Diseases
Term: 08/6/2018-01/31/2022
Professor of Pediatrics
Tufts University School of Medicine
Director, Pediatric Infectious Disease
Tufts Medical Center
Boston, MA 02111

Andrea Shane, M.D., M.P.H., M.Sc.
Expertise: Pediatric & Infectious Diseases
Term: 02/01/2018-01/31/2022
Associate Professor of Pediatrics
Division of Pediatric Infectious Diseases
Emory University School of Medicine
Atlanta, GA 30322

Archana Chatterjee, M.D., Ph.D.
Expertise: Pediatrics, Infectious Diseases
Term: 06/21/2019 – 01/31/2023
Dean Chicago Medical School
Vice President for Medical Affairs
Rosalind Franklin University of Medicine and Science
North Chicago, IL 60064
What is VRBPAC and why should I trust them?

"I'm reassured," said Dr. Paul Offit, a committee member, director of the Vaccine Education Center and an attending physician at Children's Hospital of Philadelphia. The EUA process FDA described was "much much much closer" to the full licensing process than he had thought, he said.
c. Data from Phase 3 studies should include a median follow-up duration of at least two months after completion of the full vaccination regimen to help provide adequate information to assess a vaccine’s benefit-risk profile, including: adverse events; cases of severe COVID-19 disease among study subjects; and cases of COVID-19 occurring during the timeframe when adaptive (rather than innate) and memory immune responses to the vaccine would be responsible for a protective effect.
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Development of vaccine recommendations and policies

Key Elements for Developing Evidence Based Recommendations by ACIP

- Vaccine safety
- Vaccine efficacy/effectiveness
- Burden of disease
- Implementation issues
- Economic analysis data are presented (evidence not graded, but these data are considered during policy development)
- Evidence tables are used to summarize benefits, harms, strengths, and limitations of studies

COVID-19 Work Group composition

4 ACIP voting members
Chair
Beth Bell

Consultants
- Vaccinology
- Microbiology/Immunology
- Safety
- Ethics
- Health equity

Liaison representatives
- AAFP
- American Academy of Pediatrics
- ACOG
- AGS
- ACP
- APMCN
- ASHA
- ANA
- ASHRA
- ASTHO
- CSTE
- IDSA
- NACCHO
- CFSEU
- NMCA
- SHEA
- NACI

Ex-officio/government members
- NIH
- FDA
- CMS
- BARDA

CDC participants
Co-leads: Kathleen Dooling
Sarah Mbaeyi
CDC experts
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- American Geriatrics Society
- College of Physicians
- APhA
- National Association of County and City Health Officials
- National Advisory Committee on Immunization

Ex-officio/government members
- NIH
- FDA
- CMS

CDC participants
- Co-leads: Kathleen Dooling, Sarah Mbaeyi
- CDC experts
ACIP Vote was 13-1

One dissent (Dr. Keipp Talbot): Concern was that deaths from any cause are very common in LTCFs, and so having this group in first phase could erode vaccine confidence, since inevitably some elderly will die after getting vaccinated even though it would be unlikely to be from the vaccine.
The Advisory Committee on Immunization Practices’ Interim Recommendation for Allocating Initial Supplies of COVID-19 Vaccine — United States, 2020

Kathleen Dooling, MD1; Nancy McClung, PhD1; Mary Chamberland, MD1,2; Mona Marin, MD1; Megan Wallace, DrPH1,3; Beth P. Bell, MD4; Grace M. Lee, MD5; H. Kellip Talbot, MD6; José R. Romero, MD7; Sara E. Oliver, MD1
POST-LICENSEURE SAFETY MONITORING
Rationale for Post-Licensure Vaccine Safety Monitoring

• Safety standards for vaccines are high
• Pre-licensure trials are typically not designed to
  • Detect rare adverse events
  • Monitor vaccine safety in a real-world environment
  • Assess safety in special populations (often excluded)
  • Evaluate adverse events with delayed onset

The existence of a comprehensive robust vaccine safety monitoring system can bolster confidence in the safety of vaccines

From: Frank DeStefano, CDC presentation, 30-31 May 2019
Goals of Post-Licensure Vaccine Safety Monitoring

• Rapidly identify new or rare adverse events of clinical importance

• Investigate and conduct research of possible adverse events following immunization (AEFI) to determine causality and risk factors

• Assess safety in special populations

• Provide timely and accurate data to stakeholders, including policy makers and advisory bodies

From: Frank DeStefano, CDC presentation, 30-31 May 2019
## Reactogenicity

### Data from published Phase I/II trials

**Adults 18–55 years of age**

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</tr>
<tr>
<td>Moderna¹</td>
<td></td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Fever</td>
<td></td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (27%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1 (7%)</td>
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²Walsh et al. Safety and immunogenicity of two RNA-Based COVID-19 vaccine candidates. NEJM 2020; online publication Oct 14.
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<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Mild</td>
</tr>
<tr>
<td>N=15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td></td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>5 (33%)</td>
</tr>
</tbody>
</table>

### Wellness

‘Absolutely normal’: Covid vaccine side effects are no reason to avoid the shots, doctors say

<table>
<thead>
<tr>
<th></th>
<th>30µg</th>
<th>Post-dose 1</th>
<th></th>
<th>Post-dose 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30µg</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Mild</td>
</tr>
<tr>
<td>N=12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>1</td>
<td>1 (8%)</td>
<td>—</td>
<td>—</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
<td>1 (8%)</td>
<td>2 (17%)</td>
<td>6 (50%)</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1</td>
<td>1 (8%)</td>
<td>1 (8%)</td>
<td>4 (33%)</td>
<td>3 (25%)</td>
</tr>
</tbody>
</table>


Routine systems

**Signal detection**
- VAERS (CDC & FDA)
- VA ADERS (VA)
- VSD (CDC)
- VAECS (DoD)
- VA EHR & data warehouse
- FDA-CMS (FDA & CMS)
- DMSS (DoD)

**Signal assessment**
- VSD (CDC)
- FDA-CMS (FDA & CMS)
- CISA (CDC)
- DMSS (DoD)
- VA EHR & data warehouse

New systems

**Signal detection**
- v-safe (CDC)
- BEST (FDA)
- Sentinel surveillance (DoD MTFs)
- NHSN (CDC)
- Genesis LTCF (Brown U. & NIH)

**Signal assessment**
- BEST (FDA)
- Other EHR and payer partners (FDA)

*DoD and IHS have VAERS data sharing agreements with CDC; #BEST includes most of the major partners from Sentinel PRISM*
Routine systems

- **signal detection**
  - VAERS (CDC & FDA)
  - VA ADERS (VA)
  - VSD (CDC)
  - VAECS (DoD)
  - VA EHR & data warehouse
  - FDA-CMS (FDA & CMS)
  - DMSS (DoD)

New systems

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  - Sentinel surveillance (DoD MTFs)
  - NHSN (CDC)
  - Genesis LTCEF (Brown U. & NIH)

- **signal assessment**
  - VSD (CDC)
  - FDA-CMS (FDA & CMS)
  - VA EHR & data warehouse
  - CIAA (DoD)
  - DMSS (DoD)

*DoD and IHS have VAERS data sharing agreements with CDC; #BEST includes most of the major partners from Sentinel PRISM*
Vaccine Adverse Event Reporting System (VAERS)

- Created in 1990
- Overseen jointly by CDC and FDA
- Spontaneous, voluntary, national reporting system which collects reports of adverse events occurring after vaccination
- Each year, VAERS receives ~ 30,000 reports

Ref: 1) Singleton et al. Vaccine 1999;17:2908
   2) CDC. MMWR Surveillance Summaries 2003;52(ss01);1-24.
VAERS Reports Can Be Filed Online
Who Can Report to VAERS?

• Anyone can submit a report to VAERS
  • Health care providers
  • Vaccine manufacturers
  • Vaccine recipients
  • Parents or family members of individuals who have received a vaccine

• Some providers quite familiar with VAERS, others not
The Role of VAERS

• Can help identify unanticipated, new, rare adverse events
• Monitors trends of already known adverse events
• Monitors vaccine lot safety
• If unusually high number of adverse events after particular vaccine, “focused studies in other systems are done to determine if the adverse event is or is not a side effect of the vaccine”
Limitations of VAERS

• Under-reporting; over-reporting
• No denominator of vaccine doses given
• Virtually all conditions that can be vaccine adverse events (e.g., febrile seizures, Guillain-Barré syndrome) occur at a baseline rate in population
• No comparison group
• Cannot establish cause and effect
VAERS Data Can Be Readily Misrepresented
Preliminary list of VAERS AEs of special interest*

- COVID-19 disease
- Death
- Vaccination during pregnancy and adverse pregnancy outcomes
- Guillain-Barré syndrome (GBS)
- Other clinically serious neurologic AEs (group AE)
  - Acute disseminated encephalomyelitis (ADEM)
  - Transverse myelitis (TM)
  - Multiple sclerosis (MS)
  - Optic neuritis (ON)
  - Chronic inflammatory demyelinating polyneuropathy (CIDP)
  - Encephalitis
  - Myelitis
  - Encephalomyelitis
  - Meningoencephalitis
  - Meningitis
  - Encephalopathy
  - Ataxia

- Seizures / convulsions
- Stroke
- Narcolepsy / cataplexy
- Autoimmune disease
- Anaphylaxis
- Non-anaphylactic allergic reactions
- Acute myocardial infarction
- Myocarditis / pericarditis
- Thrombocytopenia
- Disseminated intravascular coagulation (DIC)
- Venous thromboembolism (VTE)
- Arthritis and arthralgia (not osteoarthritis or traumatic arthritis)
- Kawasaki disease
- Multisystem Inflammatory Syndrome (MIS-C, MIS-A)
- Acute respiratory distress syndrome (ARDS)

*VAERS reports of AEs of special interest in blue will be clinically reviewed by CDC scientists
Overview of the Vaccine Safety Datalink (VSD)

- Created in 1995
- Collaboration between 9 medical care organizations and CDC
- > 12 million children and adults under surveillance
- Integrated delivery systems, enrolled populations, electronic health records

9 participating integrated healthcare organizations
Data on over 12 million persons per year
VSD: High Data Quality, Supports Multiple Study Designs

• Vaccine data highly accurate (unless vaccines given outside system)
• Case ascertainment
  • Search for specific electronic ICD-9 codes
  • Can confirm by manual review of electronic records
• Study designs
  • Cohort, case-control, self-control case series
  • All designs with comparison groups
• VSD can test hypotheses and make causality assessments
Preliminary list of VSD pre-specified outcomes for RCA

- Acute disseminated encephalomyelitis (ADEM)
- Acute myocardial infarction (AMI)
- Anaphylaxis
- Acute respiratory distress syndrome (ARDS)
- Arthritis and arthralgia / joint pain
- Convulsions / seizures
- Disseminated intravascular coagulation (DIC)
- Encephalitis / myelitis / encephalomyelitis / meningoencephalitis / meningitis / encephalopathy (not ADEM or TM)
- Guillain-Barré syndrome (GBS)
- Immune thrombocytopenia (ITP)
- Kawasaki disease (KD)
- Multisystem Inflammatory Syndrome (MIS-C and MIS-A)
- Myocarditis / pericarditis
- Narcolepsy / cataplexy
- Stroke – hemorrhagic and ischemic
- Transverse myelitis (TM)
- Venous thromboembolism (VTE)
- **V-safe** is a new smartphone-based active surveillance program for COVID-19 vaccine safety
  - Uses text messaging to initiate web-based survey monitoring
  - Conducts electronic health checks on vaccine recipients
    - Daily for first week post-vaccination; weekly thereafter until 6 weeks post-vaccination
    - Additional health checks at 3, 6, and 12 months post-vaccination
  - Includes active telephone follow-up through the VAERS program with vaccine recipients reporting a clinically important event during any **v-safe** health check
    - A VAERS report will be taken during telephone follow-up, if appropriate
  - Captures information on pregnancy status and enables follow-up on pregnant women
Healthcare professionals (HCPs) will play an important role in **v-safe** enrollment.

CDC asks that:
- HCPs provide a one-page information sheet* to patients at vaccination.
- HCPs counsel patients on the importance of enrolling in **v-safe**.

CDC will provide information on how to briefly counsel patients on **v-safe**.

*CDC will create an electronic version of the **v-safe** information sheet for printing.
Your role

COVID-19 vaccine safety gets stronger with your participation

Public health partners
- promote participation in v-safe ✓
- promote reporting to VAERS ✓
- communicate with your partners on vaccine safety ✓

Healthcare providers
- encourage patient participation in v-safe ✓
- report adverse events to VAERS ✓
- communicate with patients on vaccine safety ✓
Safety Considerations Specific to mRNA Vaccines

- Manufacturing process does not require chemicals or cell cultures that could become contaminated
  - Avoids the common risks associated with other vaccine platforms, like live virus, viral vectors, inactivated virus, and protein subunit
- Short manufacturing time for mRNA presents few opportunities for contamination
- Theoretical risks of infection or integration of the vector into host cell DNA are not a concern for mRNA
- Generally considered a relatively safe vaccine format
- Some theoretical concerns that have thus far not been seen
  - Example: Extracellular RNA could theoretically contribute to edema or thrombus formation
Safety Considerations Specific to mRNA Vaccines

• While the speed with which these mRNA vaccines have been developed seems fast, the technology has been in development for over 30 years.

Direct gene transfer into mouse muscle in vivo

JA Wolff, RW Malone, P Williams, W Chong, G Acsadi, A Jani, PL Felgner
+ See all authors and affiliations

Science 23 Mar 1990:
Vol. 247, Issue 4949, pp. 1465-1468
DOI: 10.1126/science.1690918
VACCINE ALLOCATION AND IMPLEMENTATION
COVID-19 incidence is highest in young adults

National Estimate of COVID-19 Incidence per 100,000 Population, by Age Group – Data through Nov 16, 2020

- 80+ years: 2949.9
- 65 - 79 years: 2009
- 55 - 64 years: 2526.5
- 35 - 54 years: 3073.3
- 25 - 34 years: 3236.3
- 18 - 24 years: 3965.2
- 14 - 17 years: 1830.4
- 6 - 13 years: 949.3
- 0 - 5 years: 727.4
COVID-19 mortality rates are highest in older adults.

National Estimate of COVID-19 Deaths per 100,000 Population, by Age Group – Data through Nov 13, 2020

- 80+ years: 648.8
- 65 - 79 years: 149
- 55 - 64 years: 51.5
- 35 - 54 years: 15.2
- 25 - 34 years: 3.3
- 18 - 24 years: 1.3
- 14 - 17 years: 0.2
- 6 - 13 years: 0.1
- 0 - 5 years: 0.2

Death Rate per 100,000 Population
Older adults in congregate settings are disproportionately affected by COVID-19

- Long-Term Care Facility (LTCF) residents and staff accounted for 6% of cases and 40% of deaths in the U.S.¹ (Nov 24, 2020)
  - Skilled Nursing Facilities (~1.3M)
    - ~496,000 confirmed + probable cases (as of Nov 15, 2020)²
    - >69,000 deaths
  - Assisted Living Facilities (~0.8M)
    - 27,965 confirmed + suspected cases (as of Oct 15/2020, based on 23 states)³
    - 5,469 deaths (as of Oct 15/2020, based on 20 states)³

---

Allocation of COVID-19 vaccine

Policy Question #2
Which groups should be recommended to receive COVID-19 vaccine ‘X’ during Phase 1?
Allocation of initial COVID-19 vaccine: Phase 1

**Science:**
- COVID-19 disease burden
- Balance of benefits & harms of vaccine

**Implementation**

**Ethics**
Allocation of initial COVID-19 vaccine: Phase 1

- Science
- Ethics

**Implementation:**
- Values of target group
- Feasibility
Allocation of initial COVID-19 vaccine: Phase 1

- **Science**
- **Implementation**
- **Ethics**

**Ethical Principles:**
- Maximize benefits & minimize harms
- Promote justice
- Mitigate health inequities
- Promote transparency
<table>
<thead>
<tr>
<th>Ethical Principle</th>
<th>Health care personnel (~21 million)</th>
<th>Long-Term Care Facility Residents (~3 Million)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maximize benefits &amp; minimize harms</strong></td>
<td>Multiplier effect- protection of HCPs and preservation of healthcare capacity</td>
<td>LTCF residents are at high risk for infection, severe disease and death from COVID-19. Prevention may reduce hospital utilization</td>
</tr>
<tr>
<td><strong>Promote justice</strong></td>
<td>HCP provide care in high-risk settings and will be essential for vaccine distribution</td>
<td>Federal Pharmacy Partnership Program will facilitate equal access to vaccine across most LTCFs</td>
</tr>
<tr>
<td><strong>Mitigate health inequities</strong></td>
<td>HCP includes broad range of occupations, inclusive of low-wage earners and racial and minority groups</td>
<td>Federal Pharmacy Partnership Program will reach LTCF across the socioeconomic spectrum</td>
</tr>
</tbody>
</table>
The Advisory Committee on Immunization Practices’ Ethical Principles for Allocating Initial Supplies of COVID-19 Vaccine — United States, 2020
<table>
<thead>
<tr>
<th>Ethical principle</th>
<th>Essential question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximize benefits and minimize harms</td>
<td>What groups are at highest risk for SARS-CoV-2 infection, COVID-19 disease, hospitalization, and death?</td>
</tr>
<tr>
<td></td>
<td>What groups are essential to the COVID-19 response?</td>
</tr>
<tr>
<td></td>
<td>What groups are essential to maintaining critical functions of society?</td>
</tr>
<tr>
<td></td>
<td>What are the important characteristics of these groups (e.g., size or geographic distribution) that might inform the magnitude of benefit based on the amount of vaccine available or its characteristics?</td>
</tr>
<tr>
<td>Promote justice</td>
<td>Does the allocation plan result in fair and equitable access of the vaccine for all groups?</td>
</tr>
<tr>
<td></td>
<td>How do characteristics of the vaccine and logistical considerations affect fair access for all persons?</td>
</tr>
<tr>
<td></td>
<td>Does allocation planning include input from groups who are disproportionately affected by COVID-19 or face health inequities resulting from social determinants of health, such as income and health care access?</td>
</tr>
<tr>
<td>Mitigate health inequities</td>
<td>Does the plan identify and address barriers to vaccination among any groups who are disproportionately affected by COVID-19 or who face health inequities resulting from social determinants of health, such as income and health care access?</td>
</tr>
<tr>
<td></td>
<td>Does the allocation plan contribute to a reduction in health disparities in COVID-19 disease and death?</td>
</tr>
<tr>
<td></td>
<td>What health inequities might inadvertently result from the allocation plan, and what interventions could remove or reduce them?</td>
</tr>
<tr>
<td></td>
<td>Is there a mechanism for timely assessment of vaccination coverage among groups experiencing disadvantage and the possibility for course correction if inequities are identified?</td>
</tr>
<tr>
<td>Promote transparency</td>
<td>How does development of the allocation plan include diverse input, and if possible, public engagement?</td>
</tr>
<tr>
<td></td>
<td>Are the allocation plan and evidence-based methods publicly available?</td>
</tr>
<tr>
<td></td>
<td>Is the allocation plan clear about what is known and unknown and about the quality of available evidence?</td>
</tr>
<tr>
<td></td>
<td>What is the process for revision of allocation plans based on new information?</td>
</tr>
<tr>
<td></td>
<td>Is there a mechanism to report demographic data elements for vaccine recipients (e.g., age, race/ethnicity, and occupation) to support equitable vaccination coverage?</td>
</tr>
<tr>
<td>Principles (with transparency across the decision-making process)</td>
<td>Candidate groups* (approximate no.)</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td><strong>Maximize benefits and minimize harms</strong></td>
<td></td>
</tr>
<tr>
<td>Preserves health care services essential to the COVID-19 response and the overall health care system</td>
<td>Health care personnel† (21 million)</td>
</tr>
<tr>
<td>Multiplier effect§</td>
<td></td>
</tr>
<tr>
<td><strong>Promote justice</strong></td>
<td></td>
</tr>
<tr>
<td>Addresses elevated occupational risk for SARS-CoV-2 exposure for those unable to work from home</td>
<td></td>
</tr>
<tr>
<td>Promotes access to vaccine across a spectrum of HCP job types and settings</td>
<td></td>
</tr>
<tr>
<td><strong>Mitigate health inequities</strong></td>
<td></td>
</tr>
<tr>
<td>Racial and ethnic minority groups are disproportionately represented in low-wage HCP§§§</td>
<td>Racial and ethnic minority groups are disproportionately represented in many essential industries***</td>
</tr>
<tr>
<td>Approximately one quarter of essential workers live in low-income families†††</td>
<td></td>
</tr>
</tbody>
</table>
ACIP Work Group Proposed Phase 1 Sequence

Phase 1c
Adults with high-risk medical conditions
Adults 65+

Phase 1b
Essential workers

Phase 1a
HCP
LTCF residents
ACIP Work Group Proposed Phase 1 Sequence

Health-care workers, nursing home residents should get coronavirus vaccine first, panel says
Health Care Personnel: Considerations for Implementation

- Health care systems and public health should work together to ensure vaccine access to health care personnel who are not affiliated with hospitals.

- Consider staggering vaccination of personnel from similar units or positions.

- Planning for personnel to have time away from clinical care if HCP experience systemic symptoms post-vaccination.

- Additional CDC guidance forthcoming:
  - Approach to systemic symptoms in HCP after COVID-19 vaccination.
Health Care Personnel:
Sub-prioritization Considerations

- Where sub-prioritization of health care personnel is needed, consider:
  - Individuals with **direct patient contact**\(^1\) and unable to telework:
    - Personnel who provide **services** to patients or patients' family members
    - Personnel who handle **infectious** materials
    - Can include inpatient or outpatient settings
  - Personnel working in residential care or long-term care facilities
  - Personnel without known infection in prior **90 days**
    - Reinfection appears uncommon during the initial 90 days after symptom onset of preceding infection\(^2\)
    - Serologic testing **not recommended** prior to vaccination

---

\(^{1}\)Within 6 feet

\(^{2}\)Duration of Isolation and Precautions for Adults with COVID-19 | CDC
Health Care Personnel:
Clinical Considerations: Pregnancy or Breastfeeding

- 75% of health care workforce are women
  - Approximately 330,000 health care personnel could be pregnant or recently postpartum at the time of vaccine implementation

- Data demonstrate potentially increased risks of severe maternal illness and preterm birth due to COVID-19 disease

- No data on use of mRNA vaccines in pregnant/breastfeeding women

- Await Phase III data, FDA assessment, EUA Conditions of Use
  - Once reviewed, anticipate further guidance around use of COVID-19 vaccines in pregnant/breastfeeding Phase 1a populations
<table>
<thead>
<tr>
<th>Phase</th>
<th>Category</th>
<th>Members</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Critical Workforce</td>
<td>Inpatient Healthcare workers, including those at assisted living facilities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Outpatient Healthcare Workers, including home health workers and outpatient pharmacists</td>
</tr>
<tr>
<td>1B</td>
<td>Critical Workforce</td>
<td>EMS, Firefighters, Police, Public Health Personnel and Correctional Workers</td>
</tr>
<tr>
<td>1C</td>
<td>Highest Risk Individuals</td>
<td>Residents/patients of assisted living, long-term care, and nursing home facilities</td>
</tr>
</tbody>
</table>
| 2A    | Congregate Housing Essential Workers | Congregate Housing:  
- Adults experiencing homelessness living in congregate shelters  
- Incarcerated adults  
- Adults living in group homes  
- Workers living in congregate settings (e.g. ski industry, some agricultural workers, etc.)  
- Students living in college dorms or other congregate housing  
  Essential workers:  
- With direct interaction with the public (e.g. grocery store workers, teachers, childcare, etc.)  
- Working in high-density settings (e.g. agricultural, meat-packing workers, etc.)  
- Serving persons that live in high-density settings (e.g. homeless shelter or group home workers) |
| 2B    | Higher Risk Individuals       | Adults 65 or older  
Adults with obesity, diabetes, chronic lung disease, significant heart disease, chronic kidney disease requiring dialysis, active cancers, and/or immunocompromised status |
| 3     | General Public                | Adults 18-64 without high-risk conditions                                                                                           |
CO Vaccination Plan Phases

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POLITICS

Gov. Polis says Colorado prisoners shouldn’t get COVID-19 vaccine before free people

Polis says Colorado will revise its vaccine distribution priority plan soon

- Students living in college dorms or other congregate housing

Essential workers:
- With direct interaction with the public (e.g. grocery store workers, teachers, childcare, etc.)
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- Serving persons that live in high-density settings (e.g. homeless shelter or group home workers)

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<td>3</td>
<td>General Public</td>
<td>Adults 18-64 without high-risk conditions</td>
</tr>
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Considerations for Children

• What is the burden of disease in children? As of Nov 26, per AAP/CHA
  • 1,337,217 cases (=1777/100K; kids are 1.3M of the 11.1M US cases)
  • 6716 hospitalizations (only 24 states report; as of 11/19)
  • 138 deaths

• Disproportionate burden in minority communities: about 20% of deaths have been in White children

• MIS-C?

• Conundrum for families and providers if safe and effective vaccines available for adults but no data in children

• What to do about high risk older children? What will FDA say? What will ACIP say?
September 29, 2020

Alex Azar, JD
Secretary
U.S. Department of Health and Human Services
200 Independence Avenue, SW
Washington, DC 20201

Stephen M. Hahn, M.D.
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Secretary Azar and Commissioner Hahn:
Letter from the AAP President

• AAP represents 67,000 providers of healthcare to children
• ...“how crucial it is for children to be included in vaccine trials of SARS-CoV-2 vaccines.”
• Letter refers to the potential direct and indirect benefits of the vaccines.
• It is “counter to the ethical principle of distributive justice to allow children to take on great burdens during this pandemic” without “the opportunity to benefit from a vaccine, or to delay that benefit” because they are not included in trials.
• Urges careful trials with rigorous oversight and review.
Conclusions

• Although we are in for a dark winter, vaccines to prevent COVID-19 offer a potential end to this pandemic in this historic moment
• The first vaccine candidates at this point appear to be both safe and highly effective
• Although the vaccine trials have happened with unprecedented speed, we have reasons to “trust the process”
• Vaccine confidence among HCWs will be crucial to the future of these vaccines
• Allocation and distribution must follow the ethical principles of maximizing benefits and minimizing harms, promoting justice, and mitigating health inequities
Conclusions

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• The first vaccine candidates at this point appear to be both safe and highly effective
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• Vaccine confidence among HCWs will be crucial for these vaccines
• Allocation and distribution must follow the ethical principles of maximizing benefits and minimizing harms, promoting justice, and mitigating health inequities

Roll up your sleeves!
Resources

• https://www.washingtonpost.com/health/2020/11/17/covid-vaccines-what-you-need-to-know/?arc404=true
• https://www.immunizecolorado.org/