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Biomedical Engineering +
Leonard Gelfand Center

Vaccine Development and the COVID-19 Pandemic

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This educational resource for high school audiences was developed as a project by Carnegie Mellon student, Avika Bansal and Claire Kenny, for the course *Experiential Learning through Projects*, Section O, taught by Dr. Conrad Zapanta and Dr. Judith Hallinen during the summer of 2020.

Editing and additional project development was completed by Claire Kenny.

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Vaccine Development: Key Terms

Vaccine [1]: A product that stimulates a person's immune system to produce immunity to a specific disease, protecting the person from that disease.

Vaccine Engineering [2]: Engineering approach to discover novel antigens, epitopes, and adjuvants that can stimulate and manipulate the immune system, as well as their targeted delivery, for the prevention and treatment of important diseases such as cancer and infectious diseases

Antigen [3]: Molecules capable of stimulating an immune response, with each having distinct surface features (or epitopes) resulting in specific responses

Antibody [3]: (also known as immunoglobulins) Y-shaped proteins that have the ability to recognize and bind to antigens

Adjuvants [4]: Components capable of enhancing and/or shaping antigen-specific immune responses.

Immunogenicity [5]: A therapy's tendency to trigger an unwanted immune response against themselves

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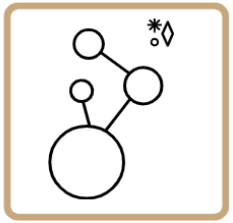
Vaccine Engineering: Areas of Focus

Antigen Discovery

- Largely done by computer scientists and bioinformaticians
- Need to curate and standardize existing and new data

Engineered Nanoparticles

- Stabilize vaccines
- Can double as an adjuvant
- Regulate the route of entry into antigen presenting cells



Engineered Adjuvants

- Enhance and stabilize vaccine-induced responses
- Selectively add well-defined molecules, formulations or both

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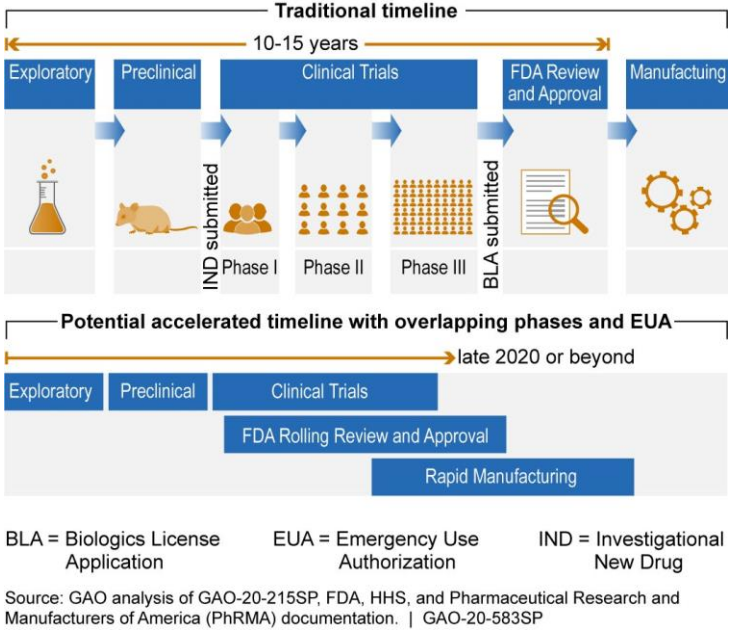
The Vaccine Development Process (Can take 10-15 years)

General vaccine development steps as given by the CDC:

1. Exploratory stage
2. Pre-clinical stage
3. Clinical development (3 Phase Process)
4. Regulatory review and approval
5. Manufacturing
6. Quality control



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Step 1: An Investigational New Drug Application (IND)

Describes the vaccine, its method of manufacture, and quality control tests for release

Step 3: A Biologics License Application (BLA)

Must provide the multidisciplinary FDA reviewer team with the efficacy and safety information necessary to make a risk/benefit assessment and to recommend or oppose the approval of a vaccine

Step 5: Presentation of Findings to FDA's Vaccines and Related Biological Products Advisory Committee External (VRBPAC)

Non-FDA expert committee provides advice to the Agency regarding the safety and efficacy of the vaccine for the proposed indication

Step 0: Pre-Clinical Trials

Assessment as to whether the product is reasonably safe for initial testing in humans

Step 2: Pre-licensure Vaccine Clinical Trials

Includes 3 stages to determine the safety and efficacy of the vaccine, must provide benefits that outweigh the costs

Step 4: Inspection of the Manufacturing Facility

During this stage, the proposed manufacturing facility undergoes a pre-approval inspection during which production of the vaccine as it is in progress is examined in detail.

Step 6: Usability testing of product labeling

Includes potential benefits and risks, to communicate with patients and parents, and to safely deliver the vaccine to the public

Let's Take a Closer Look at the Timeline…

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Exploratory Stage (2-4 years)

- Basic laboratory research
- Can include identifying natural or synthetic antigens that might help prevent or treat a disease

Pre-Clinical Stage (1-2 years)

- Tissue-culture or cell-culture systems
- Animal testing
  - Assess the safety of the candidate vaccine and its immunogenicity, or ability to provoke an immune response
  - Rats and monkeys

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Clinical Development

Phase I
(several months)

- Small group of **adults** (20-80 subjects)
- Non-blinded
- ***Goal***: Assess the safety and determine the type and extent of immune response

Phase II
(up to 2 years)

- Larger group of subjects (several hundred)
- Randomized and well controlled
- ***Goal***: Study the vaccine's safety, immunogenicity, proposed doses, schedule of immunizations, and method of delivery.

Phase III
(1-3 years)

- Thousands to tens of thousands of subjects
- Randomized and double blind
- Followed by a Biologics License Application to the FDA
- ***Goal:*** Assess vaccine safety in a large group of people, vaccine efficacy

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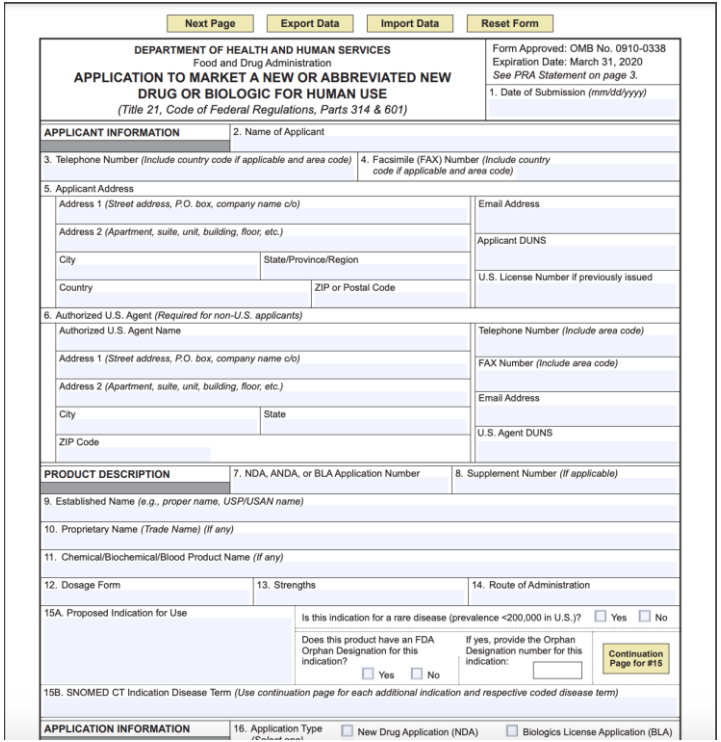
Regulatory Review and Approval (up to 3 years)

- Includes a Biologics License Application (BLA) and Product License Application (PLA)
- Presentation of clinical trial findings
- Presentation to a non-expert audience



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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
APPLICATION TO MARKET A NEW OR ABBREVIATED NEW DRUG OR BIOLOGIC FOR HUMAN USE
(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2020
See PRA Statement on page 3.

1. Date of Submission *(mm/dd/yyyy)*

APPLICANT INFORMATION

2. Name of Applicant

3. Telephone Number *(Include country code if applicable and area code)*

4. Facsimile (FAX) Number *(Include country code if applicable and area code)*

5. Applicant Address

Address 1 *(Street address, P.O. box, company name c/o)*

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

City | State/Province/Region

Country | ZIP or Postal Code

Email Address

Applicant DUNS

U.S. License Number if previously issued

6. Authorized U.S. Agent *(Required for non-U.S. applicants)*

Authorized U.S. Agent Name

Address 1 *(Street address, P.O. box, company name c/o)*

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

City | State

ZIP Code

Telephone Number *(Include area code)*

FAX Number *(Include area code)*

Email Address

U.S. Agent DUNS

PRODUCT DESCRIPTION

7. NDA, ANDA, or BLA Application Number

8. Supplement Number *(If applicable)*

9. Established Name *(e.g., proper name, USP/USAN name)*

10. Proprietary Name *(Trade Name) (If any)*

11. Chemical/Biochemical/Blood Product Name *(If any)*

12. Dosage Form | 13. Strengths | 14. Route of Administration

15A. Proposed Indication for Use

Is this indication for a rare disease (prevalence <200,000 in U.S.)? ☐ Yes ☐ No

Does this product have an FDA Orphan Designation for this indication? ☐ Yes ☐ No

If yes, provide the Orphan Designation number for this indication:

Continuation Page for #15

15B. SNOMED CT Indication Disease Term *(Use continuation page for each additional indication and respective coded disease term)*

APPLICATION INFORMATION

16. Application Type ☐ New Drug Application (NDA) ☐ Biologics License Application (BLA)

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Manufacturing

- Proposed manufacturing facility undergoes a pre-approval inspection
- Upon approval the company begins production of the actual vaccine

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Quality Control

- Check the consistency in the production of vaccine
- Each batch of the product is of the same quality and specifications of the batch that has been tested
- Each batch is shown to be safe and efficacious in research

National Institutes of Health (NIH):
- multi-PI grants
- PPG
- NCRR
- RFAs
- Contracts (IEDB)

Pharmaceutical Industry:
- Research contracts
- Licensing

All of this needs funding…

Where would we look?[2]

Biotech Industry:
- Funding for IP
- Startups
- Angel investors
- Venture capitalist companies

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So how does this relate to the SARS/COVID-19 pandemic?

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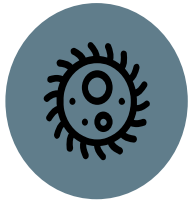
Analyzing a Virus to Determine Treatment

Where Viruses are in the Environment

How they jump from animals to people

How they spread through a population

How they interact with the human body



Coronavirus Background

Coronaviruses are respiratory diseases, and the cause of the common cold, otherwise known as “mild upper respiratory tract infection”

Severe Rcute Respiratory Syndrome (SARS)	2003	Animals to people	Severe symptoms but not easily spread
Middle East Respiratory Syndrome (MERS)	2012	Camels to people	Severe symptoms but not easily spread
SARS coronavirus-2 (SARS2)	2019	Animals to people	Severe symptoms, and easily spread

Contained in the Middle East

Emerging infectious disease means humans have no immunity

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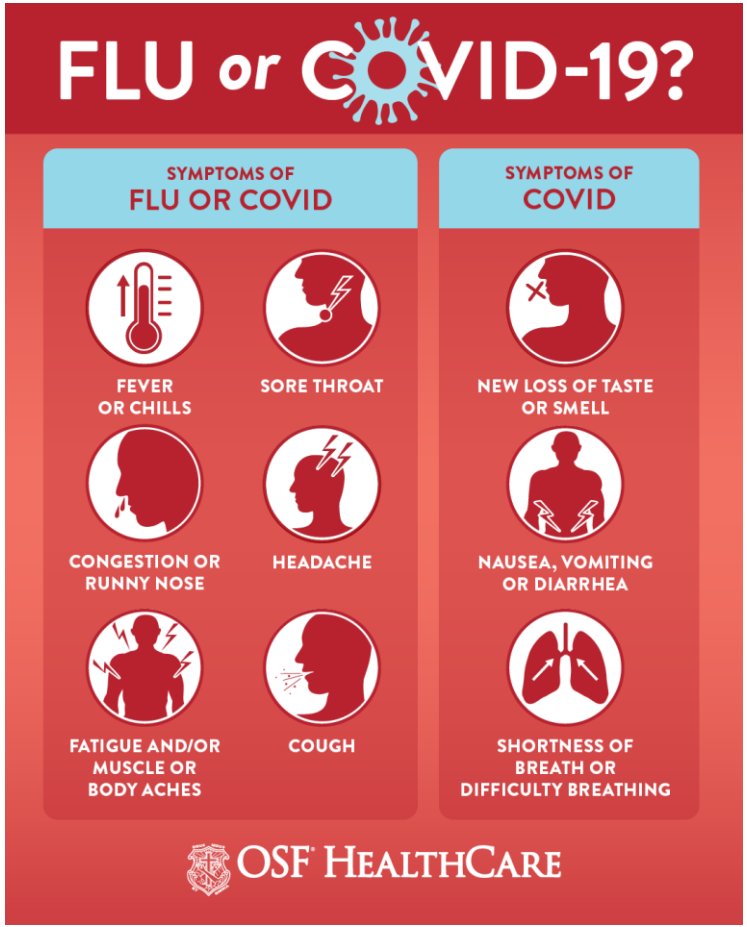

COVID-19 symptoms

2-14 day incubation period before symptoms show

- Fever/chills
- Cough
- Loss of taste/smell
- Nausea
- Diarrhea
- Difficulty breathing *
- Bluish fingers *
- Pain in chest *

*signs to go to hospital

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Treatment Plans

Doctors will perform:

- Chest x ray
- CT scan to view lung tissue
- Blood tests
- Etc.

To determine if these are needed:

- Supplemental oxygen
- Mechanical ventilation
- Antibiotics
- IV fluids
- Etc.

Risks of the SARS/COVID-19 Vaccine

The SARS/COVID-19 Vaccine comes with the potential issues of:

- **Antibody-dependent enhancement (ADE)**, in which a vaccine may actually worsen the consequences of the disease rather than protect
- Those most at risk are over 60, with **resistance to vaccination** beginning as early as 30
- May reduce the chance of getting the disease (and its symptoms) but **not prevent infection**
- **New variants** being less susceptible

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“The moment you get a vaccine doesn’t mean you’re going to put your mask in the trash. The reality is there’s probably going to have to be different generations of vaccines”

Maria Elena Bottazzi
Vaccine Developer at Baylor College of Medicine

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SARS/COVID-19 Vaccine in the US

Research:

- Funding is plentiful
- There are many different approaches being studied
- High amount of collaboration between small firms developing the vaccines and large drug companies that can mass produce

Original Plan for the Vaccine:

- The administration has promised to give the vaccine free to “vulnerable” people who cannot afford it
- There will be a tiered approach to distribute the vaccine: older people, people with pre-existing conditions, and health care workers.

3 Main Vaccines Currently Approved in the US

- ModernaTX, Inc.
- Pfizer Inc.
- Johnson & Johnson

* There are other vaccines in use in other countries.

mRNA-1273

ModernaTX, Inc.

- Uses **messenger RNA,** an approach that does not require a virus to make the vaccine
- **Dosage**: 2 shots, one month (28 days) apart
- **Effectiveness**: 94.1%
- **Minimum Age:** 18+
- **Common Side Effects:** Chills, tiredness, headache, pain in area of shot
- **Duration of Protection**: Unknown

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BNT162b2

Pfizer-BioNTech

- Uses **messenger RNA,** an approach that does not require a virus to make the vaccine
- **Dosage**: 2 shots, 21 days apart
- **Effectiveness**: 95%
- **Minimum Age:** 16+
- **Common Side Effects:** Chills, tiredness, headache, pain in area of shot
- **Duration of Protection**: Unknown

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JNJ-78436735 or Ad26.COV2.S.

Johnson & Johnson

- Is an **Adenovirus-Based Vaccine**, which uses non-enveloped, double-stranded DNA viruses
- **Dosage**: 1 shot
- **Effectiveness**: 62% against moderate-severe cases, ~100% against hospitalization and death
- **Minimum Age:** 18+
- **Common Side Effects:** Chills, tiredness, headache, nausea, pain in area of shot
- **Duration of Protection**: Unknown

Decisions, Decisions

So how do we decide the best way to distribute the vaccine?

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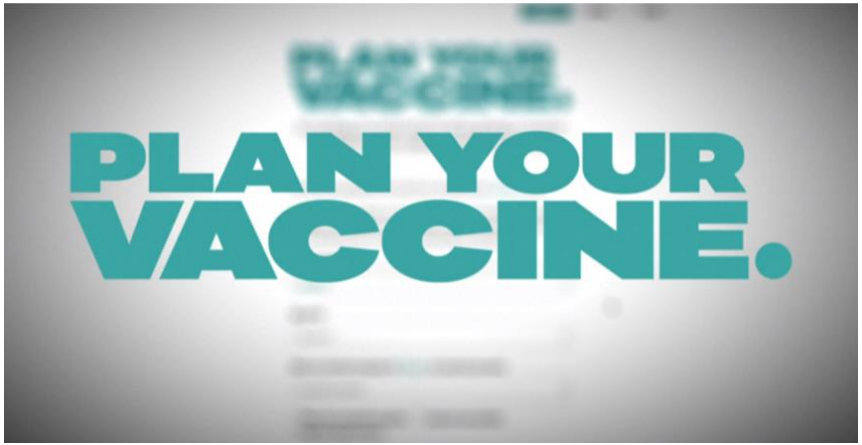
Allocation Considerations

The allocation of the vaccine shifts depending on the…

- Supply
- Demand
- Vaccine characteristics
- Disease epidemiology

The federal government determined the amount of vaccines designated for each jurisdiction, with each jurisdiction's immunization program responsible for managing and approving the orders and implementation.



Allocation Disparities

Looking at the spring 2021 system of vaccine allocation and distribution: there were numerous disparities seen between different areas. Examples include the following:

- Oregon is prioritizing teachers over the elderly (approach that could help schools and businesses reopen)
- New Jersey has put smokers ahead of educators (which could save lives)

Why might these disparities occur?

- There are different circumstances and situations
- Federal, states, and local health departments as well as medical centers have each developed different allocation formulas, based on a variety of ethical and political considerations
- Some areas may have greater numbers of a certain population, such as there being more elderly than educators

The United States used a phased approach.

Phase 1

Potentially limited supply of COVID-19 vaccine doses available

- Focus on *critical populations*
- Ensure vaccination locations can reach populations and manage cold chain requirements

Phase 2

Large number of vaccine doses available

- Access to vaccine for all critical populations not vaccinated in Phase 1
- Attempt to reach the general population
- Expand provider network

Phase 3

Surplus of doses

- Ensure equitable vaccination across the entire population
- Monitor vaccine situation
- Reassess strategy to increase uptake in areas with low coverage

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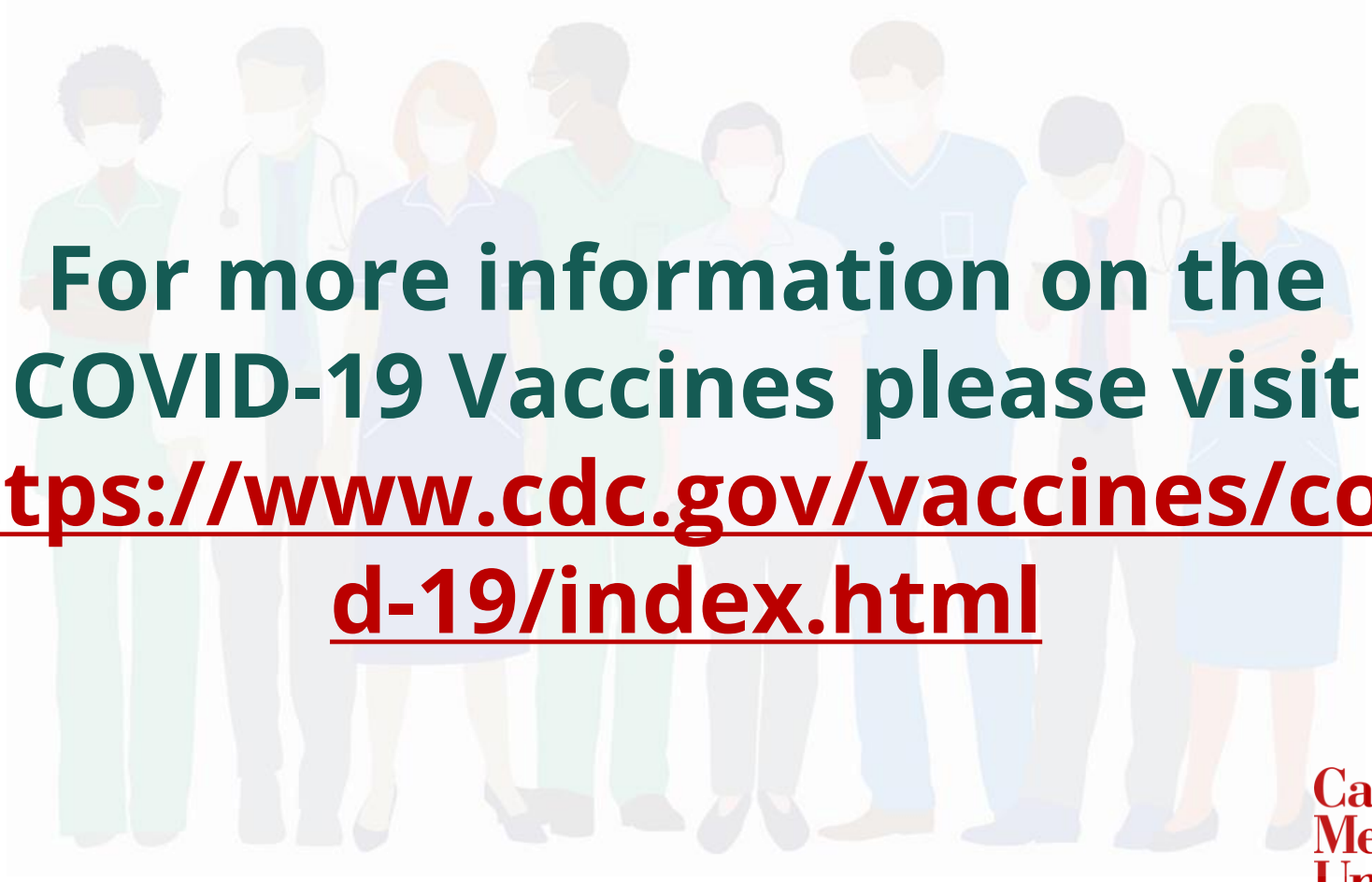

For more information on the COVID-19 Vaccines please visit https://www.cdc.gov/vaccines/covid-19/index.html

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