Vaccines against SARS-CoV-2
Progress and Prospects

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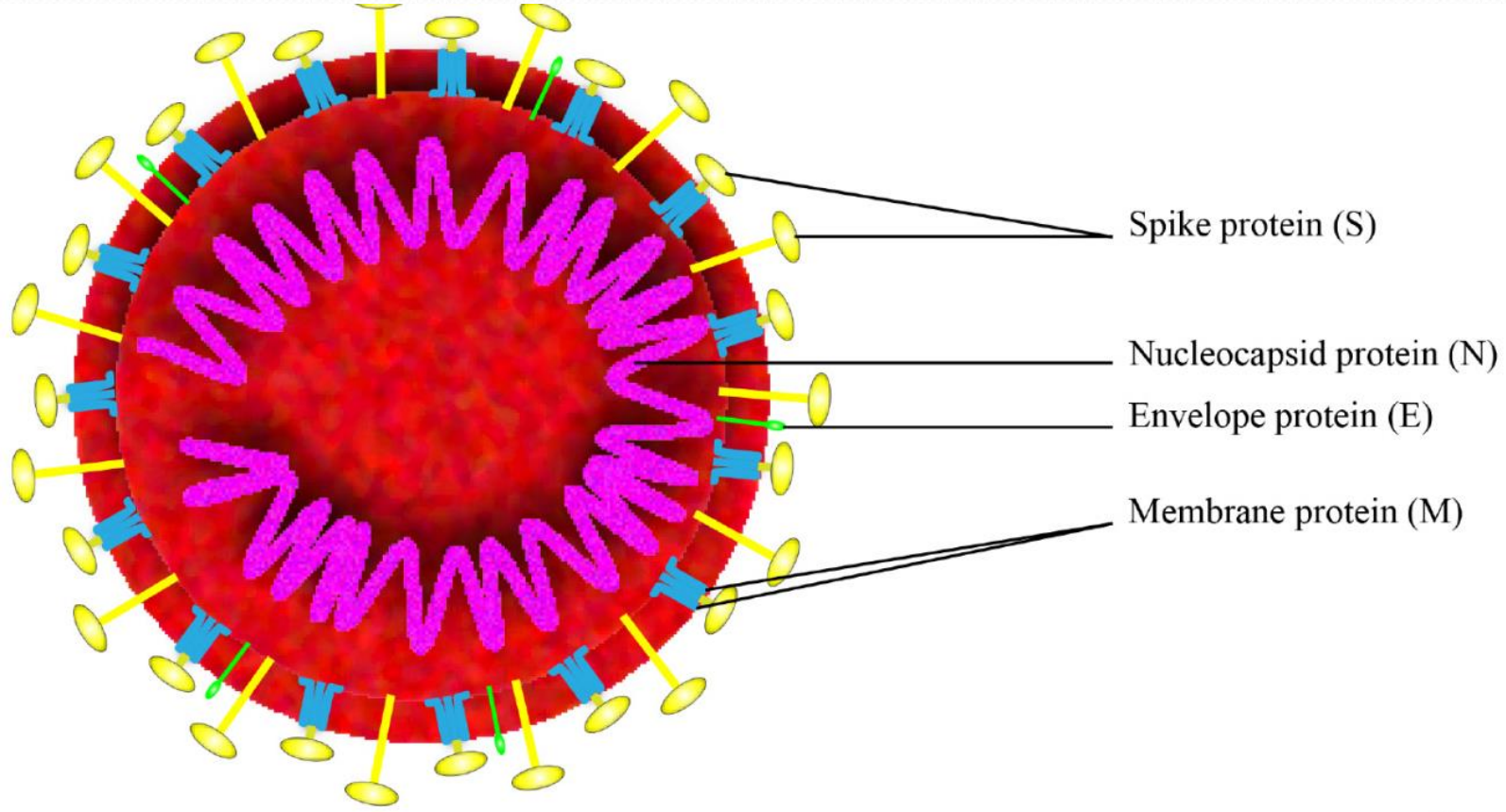
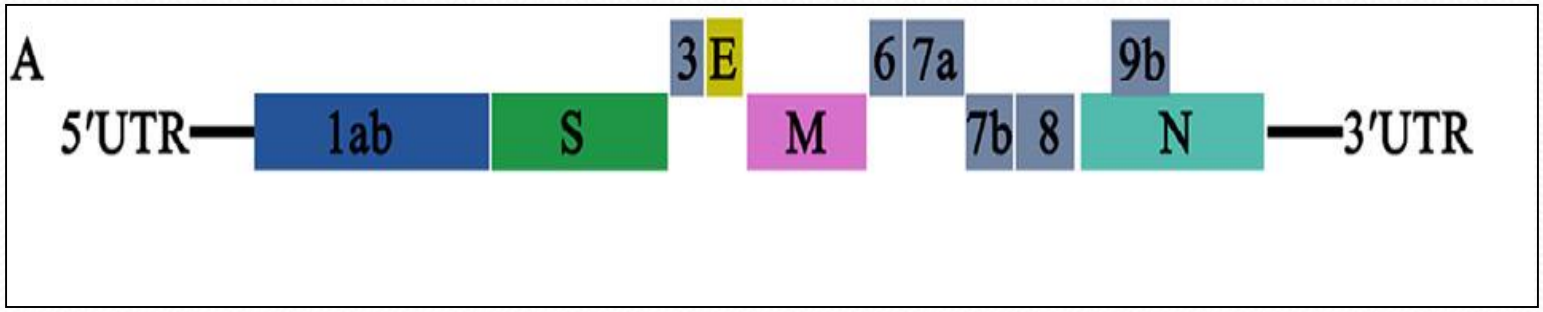
General information

SARS-CoV-2 is a positive-strand RNA virus



Genome



- 5’ end long ORF1ab encode 15 or 16 **non-structural** proteins

- 3’ end encodes 4 major **structural proteins**:
  - Spike (S)
  - Nucleocapsid (N)
  - Membrane (M)
  - Envelope (E)

Why Vaccination?

- Vaccines are the **most effective** and **economical** means to prevent and control infectious diseases
- The epidemic is **still spreading** all over the world
- SARS-CoV-2 infection may become a flu-like **seasonal disease** and coexist with human beings for a long time.
- So far, **more than 70** companies/ institutions have launched their programs on vaccine developments

Which kind of immune responses?

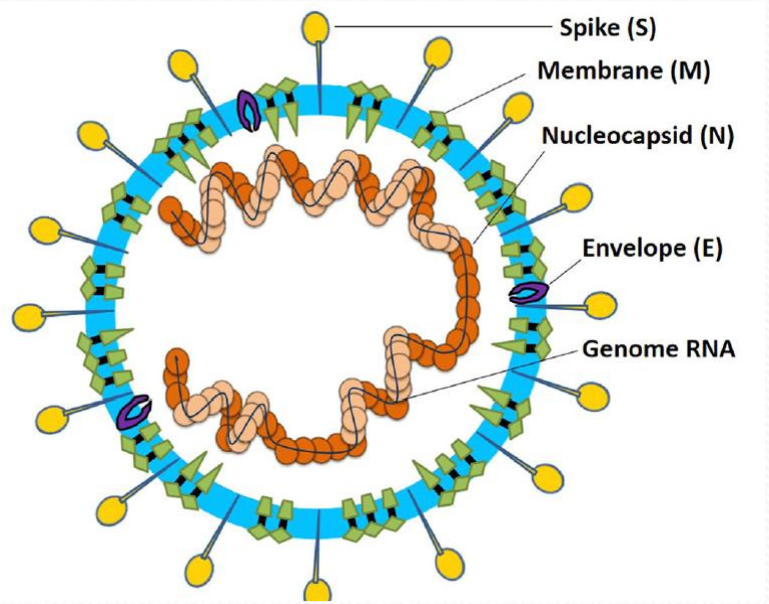
- **Unknown**
- **Antibodies**, prevent viruses from entering cells
- **T cells**—which clear infected cells—proved a better correlate of immunity in monkey studies on MERS

- Having **a balance of antibody and T cell** responses probably is the best approach

Antigen Selection

Antigens

- 1- Whole Cell Antigens
- 2- Spike Protein
- 3- Nucleocapsid Protein
- 4- Membrane Protein
- 5- Envelope Protein



Whole Cell Antigens (WCA)

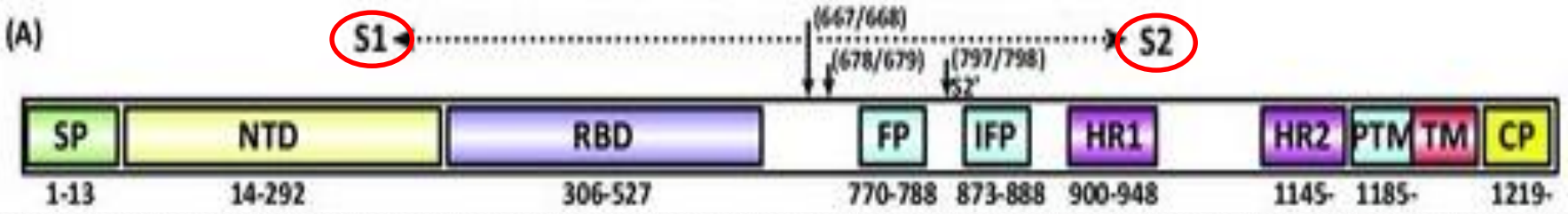
- WCA contain **all the elements** of the virus
- Previously applied for developing other vaccines

- Several institutions have started WCA vaccine development for SARS-CoV-2

- Limitations:

  Difficulties in **quality control**

  Difficulties in **consistency** evaluation



Antigens based on S protein

1- Full-Length **S** Protein

2- Receptor binding domain (**RBD**)

3- N-terminal domain (**NTD**)

4- **S1** (contains both RBD and NTD)

5- Fusion peptide (**FP**)

Why S protein?

- S protein is currently **the most promising antigen** because:

- 1- It is **surface exposure** and thus is able to be directly recognized by host immune system

- 2- It mediates **the interaction with host cell** by binding to the receptor ACE2

- 3- The homologue proteins were **already used** for vaccine development against SARS and MERS, and were proved to be effective

Full-Length S Protein

- Previously immunization with S protein against other coronaviruses showed **neutralizing antibodies** and **protection** in **mice.**

- Clover Biopharmaceuticals constructed a S protein trimer vaccine that its further preclinical safety and analysis will be launched within the next weeks.

RBD (Receptor Binding domain)

- RBD immunization induced specific **antibodies** that may block virus invasion.
- RBD is relatively conserved
- RBD contain multiple conformational **epitopes**
- RBD was used in the development of SARS and MERS vaccines.

Most of SARS-CoV-2 **subunit** vaccines currently under development use **RBD** as the antigen

NTD (N-terminal domain)

- NTD shows carbohydrate receptor-binding activity
- NTD induced potent **cellular** immunity and **antibodies** against MERS-CoV in mice
- However, it is not as conserve as RBD

S1 Subunit

- It contains **both RBD and NTD**
- It is mainly involved in the binding to the host receptor.
- It is also widely used in vaccine development against coronaviruses in mice

FP

- It is involved in the **membrane fusion** of the virus

  Tianjin University has constructed an **RBD-FP** fusion protein, and high titer of antibodies was detected in **mice** and the efficacy is under evaluation.

Nucleocapsid Protein (N Protein)

- It is the **most abundant protein** in coronaviruses
- It is normally **highly conserved**
- It is **highly antigenic** (89% of patients who developed **SARS**, produced antibodies to this antigen)
- Its **DNA vaccine** generated strong humoral and cellular immune responses in mice
- However, a research indicated that it did not make significant antibody response and provided **no protection** to infection in **hamsters**

Membrane Protein (M Protein)

- It is a trans-membrane glycoprotein
- It is involved in **virus assembly**
- It is the most abundant protein on the **surface**
- It is **highly conserved**
- It contains a T cell epitope cluster that is able to induce a strong **cellular** immune response

Envelope Protein (E Protein)

- E protein is not suitable for use as an immunogen because it has been reported that **its immunogenicity is limited**.

Vaccine candidates

Vaccines under development

1. Whole-Cell Killed and Live-Attenuated Vaccines
2. Subunit Vaccines
3. mRNA Vaccines
4. DNA vaccines
5. Live vector vaccines
6. Synthetic Peptide or Epitope Vaccine

Whole-Cell Killed and Live-Attenuated Vaccines

- They present **multiple antigenic components** and can induce **diverse** immunologic effectors

- They are **traditional** vaccines with **mature** preparatory technology, and **may become the first** SARS-CoV-2 vaccine put into clinical applications.

- Lung and liver damage in some cases in a mouse model

Most Involving institutions:

Wuhan Institute of Virology

Codagenix, Inc. (USA) -Serum Institute of India

Subunit Vaccines

- Subunit vaccines include **one or more antigens** with strong immunogenicity
- They are **safer** and **easier** to produce
- Often requires the addition of **adjuvants** to elicit immune response

Most Involving institutions:

Several institutions including:

- University of Queensland
- Clover Biopharmaceuticals Inc.
- Novavax, Inc.
- Johnson & Johnson, Pasteur Institute, and Chongqing Zhifei Biological Products Co., Ltd.

- Almost all of them use the **S protein** as antigens

mRNA Vaccines

- mRNA vaccines represent a **promising alternative** to conventional vaccine approaches

  Advantages:

  high potency,

  short production cycles,

  low-cost manufacturing

  safe administration

  Limitation: Particularly, no mRNA vaccine has yet entered the market, thus it may take more time in quality standards establishment and safety evaluation.

mRNA Vaccines

- **Most Involving institutions :**

❑ **Moderna**

- mRNA-1273, encoding S protein
- It is just started **clinical trials**

❑ **Others**

- Fudan University , Shanghai Jiaotong University ,Bluebird Biopharmaceutical Company ,German biopharmaceutical company CureVac AG, Stermirna Therapeutics, BDGENE Therapeutics, Guanhao Biotech, ZY Therapeutics Inc., CanSino Biologics Inc., Baylor College of Medicine, University of Texas, Tongji university

DNA vaccines

Advantages

- They are superior to mRNA vaccines in the formulations needed for stability and delivery efficiency,

Limitation

- They need to enter the nucleus that may bring in the risk of vector integration and mutations in the host genome.

- **Most Involving institutions :**

❑ **Inovio Pharmaceuticals**

- Termed INO-4800,
- It is in phase I clinical trials.

❑ **Applied DNA Sciences Subsidiary, LineaRx, and Takis Biotech**

- Their DNA vaccine is now in preclinical studies.

Live vector vaccines

- They are live viruses (the vector) that express a heterologous antigen(s).
- **Advantages**:
- Strong immunogenicity of live attenuated vaccines
- Safety
- Widely used to induce cellular immunity in vivo

- **Most Involving institutions :**

❑ **Johnson & Johnson**

- adenovirus vector vaccine

❑ **Houston-based Greex Inc**

- adenovirus vector vaccine
- It should have now moved to animal testing

❑ **Tonix Pharmaceuticals**

- based on Horsepox Virus (TNX-1800).

Synthetic Peptide or Epitope Vaccine

They contain only certain fragments of intact antigens

Advantages

- They are easier in preparation and quality control.

Limitation

- **Lower immunogenicity**
- **Structural modifications, delivery systems,** and **adjuvants** are additionally required

Most Involving institutions:

- Hong Kong University of Science and Technology
- Generex Biotechnology

5 candidate vaccines in clinical evaluation

Platform	Type of candidate vaccine	Developer	Coronavirus target	Current stage of clinical evaluation/regulatory status- Coronavirus candidate	Same platform for non-Coronavirus candidates
Non-Replicating Viral Vector	Adenovirus Type 5 Vector	CanSino Biological Inc./Beijing Institute of Biotechnology	COVID-19	Phase 2 ChiCTR2000031781 Phase 1 ChiCTR2000030906	Ebola
DNA	DNA plasmid vaccine Electroporation device	Inovio Pharmaceuticals	COVID-19	Phase 1 NCT04336410	Lassa, Nipah HIV Filovirus HPV Cancer indications Zika Hepatitis B
Inactivated	Inactivated	Beijing Institute of Biological Products/Wuhan Institute of Biological Products	COVID-19	Phase 1 ChiCTR2000031809	
Inactivated	Inactivated + alum	Sinovac	COVID-19	Phase 1	SARS
RNA	LNP-encapsulated mRNA	Moderna/NIAID	COVID-19	Phase 1 NCT04283461	multiple candidates

71 candidate vaccines in preclinical evaluation

Challenges

Means of Efficacy Evaluation

- **Animal models** are essential for preclinical evaluation of the efficacy of vaccines.
- SARS-CoV-2 is a new pathogen and few animal models are currently available:
  - **Transgenic mice**
  - **Primate macaques**

Adjuvants

- In addition to live attenuated vaccines and live vector vaccines, **adjuvants** are required to enhance the immune response in the development of other types of vaccines.

- **Most popular adjuvant used**
  - Alum
  - MF59, an oil-in-water emulsion
  - Adjuvant system (AS) series …..developed by GlaxoSmithKline (GSK)

- A combination of different types of adjuvants could be applied to improve the immune efficacy.

Other challenges

- **Vaccine-related diseases**

  Lung disease

  Liver disease

  Antibody-dependent enhancement (ADE) responses
- **Uncertainty of protection mechanisms**

  The potential duration of immunity is unknown

  Whether single-dose vaccines will confer immunity is uncertain
- **Money**

Other challenges

- Potential difference and/or low efficacy of the vaccine in populations **different** from the clinical trials' populations

- Moreover, in a high-mortality situation, **populations may not accept** randomized, controlled trials with placebo groups

Other challenges

- Recently, there is report that **149 sites of mutations** were identified across the genome of 103 sequenced strains of SARS-CoV-2, and the virus had evolved into two subtypes, termed **L and S** subtype.

- The study also indicated that the two subtypes showed **great differences in geographical distribution**, transmission ability, and severity of disease, which add more difficulties for vaccine design

Newly emerging viruses

- If the vaccine candidate is sufficiently closely related, sequences for the **vaccines could be quickly switched** and the vaccines for the newly emerging viruses could be swiftly produced

Vaccination of older individuals

- Because older individuals are more affected, it will be important to develop vaccines that protect them
- Unfortunately they typically respond **less** well to vaccination because of immune senescence
- Formulations should include **more antigen** or **an adjuvant**

- They could still benefit indirectly if vaccination is able to **stop transmission** of the virus in younger individuals

When?

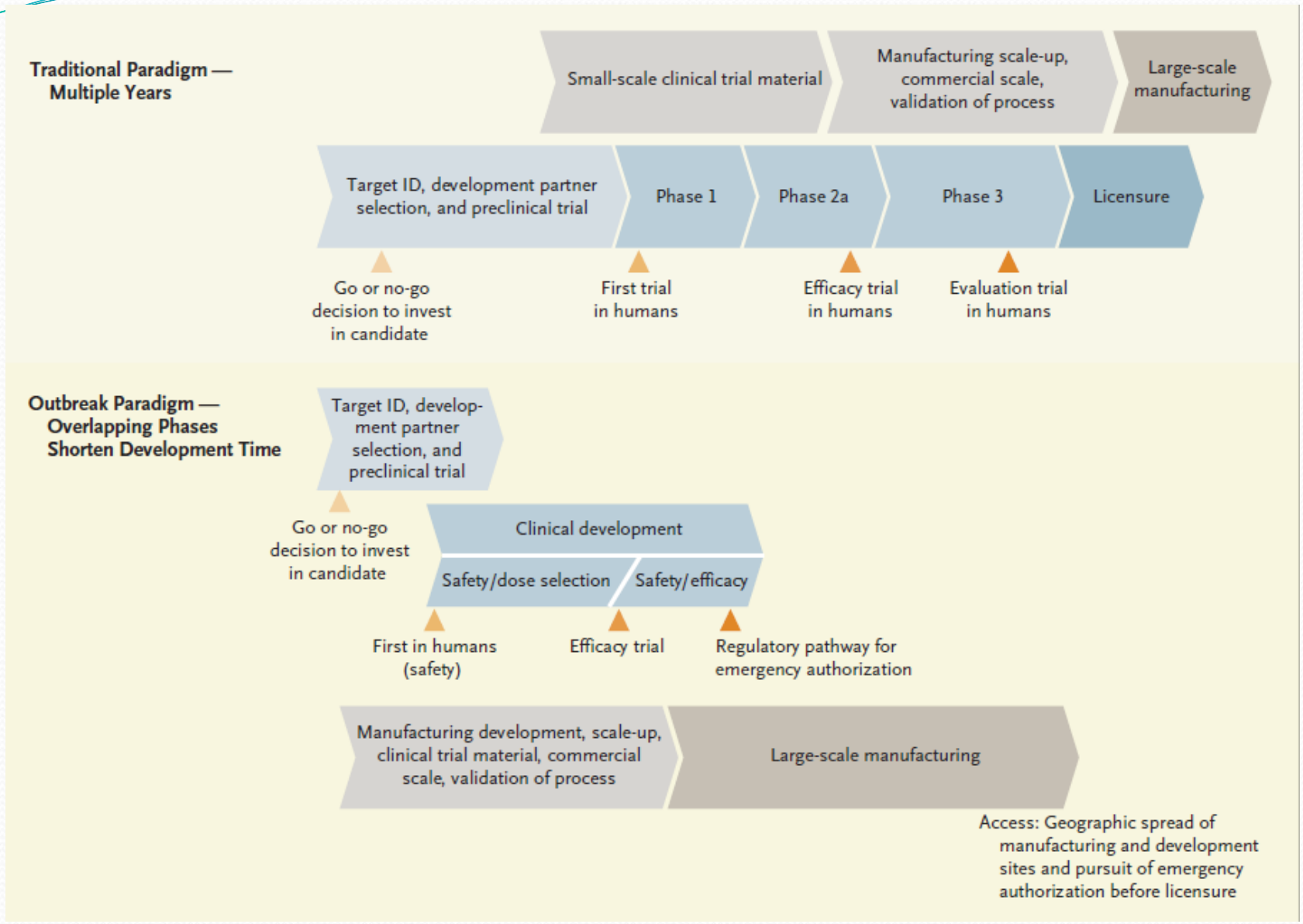
When?

- NIAID, J&J and Moderna predict a vaccine is going to take **a year, a year and a half, at least**.

  Side effects, dosing issues, and manufacturing problems can all cause delays.

- **Realistically, SARS-CoV-2 vaccines will not be available for another 12–18 months.**

- A vaccine to **health care workers** and **others at high risk** even before final efficacy trials are completed.


Traditional Paradigm — Multiple Years
Small-scale clinical trial material
Manufacturing scale-up, commercial scale, validation of process
Large-scale manufacturing
Target ID, development partner selection, and preclinical trial
Phase 1
Phase 2a
Phase 3
Licensure
Go or no-go decision to invest in candidate
First trial in humans
Efficacy trial in humans
Evaluation trial in humans
Outbreak Paradigm — Overlapping Phases Shorten Development Time
Target ID, develop-ment partner selection, and preclinical trial
Go or no-go decision to invest in candidate
Clinical development
Safety/dose selection
Safety/efficacy
First in humans (safety)
Efficacy trial
Regulatory pathway for emergency authorization
Manufacturing development, scale-up, clinical trial material, commercial scale, validation of process
Large-scale manufacturing
Access: Geographic spread of manufacturing and development sites and pursuit of emergency authorization before licensure

Why does this take so long? (other reasons)

- There is **no approved human coronavirus** vaccines.
- Many technologies used (production platforms, vectors, etc.) **are new** and need to be tested horoughly for safety.
- It takes time to **distribute** vaccines and administer them.
  - Vaccinate a large proportion take time
  - It is highly likely that more than one dose of the vaccine will be needed

Investment funds

- The **commercial markets are quite limited** due to the **high cost** and **time** required
- **CEPI** (Coalition for Epidemic Preparedness Innovations) was launched in 2017 to link academics and pharmaceutical companies and to provide financial support for the development of vaccines
- In February, 2020, **the World Bank** and **CEPI**, co-hosted a global consultation on COVID-19 vaccination.
- CEPI has invested nearly **$30 million** in vaccine development at Moderna, Inovio, and six other groups
- CEPI estimates that developing up to three vaccines in the next 12–18 months will require an investment of at least **US$2 billion.**
- This estimate does not include the costs of manufacture

Past decade epidemic vaccines

- H1N1 influenza..... vaccine was developed after 6 months
- Ebola.....epidemics ended before vaccine development was complete
- Zika.....epidemics ended before vaccine development was complete
- **SARS-CoV-2**

Ensuring global access to COVID-19 vaccines

- Involving companies do not currently have **the capacity** to produce the number of doses needed
- High-income countries **must not monopolies** the global supply of COVID-19 vaccines. This risk is real: during the 2009 influenza A/H1N1 pandemic, rich countries negotiated large advance orders for the vaccine, crowding out poor countries.

Prospects

Prospects^{-1}

- We know very little about SARS-CoV-2.
- There are more questions than answers
- The immune response of the host remains unclear
- Recently, more and more countries announced their program on COVID-19 vaccine
- However, **vaccine development has its own rules**, and **vaccine could not be achieved overnight.**

Prospects-2

- Generally, three phases of clinical trials will be carried out to evaluate the **safety**, **immunogenicity**, and **efficacy** of the vaccine.
- Typically, the development of novel vaccines generally takes **10–20 years**
- The success rate is **less than 10%,** even for a vaccine that enters clinical trials.
- In the past 30 years, the US **FDA** has approved a total of nearly **3,000 clinical trials** on vaccine applications and **less than 20 vaccines** were approved for the market.

- **Drugs are ongoing**, beside it the rapid development of a **vaccine** is a powerful means to defeat SARS-CoV-2.

- In addition, lessons learned from handling this outbreak will allow us to be better prepared in the future. **The viruses will keep coming**.

- Nobody knows which vaccines are going to work

Attempts are continuing

Yes, We can defeat COVID-19