In the name of God

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COVID 19 ; new facts;
March 11, 2021

- Used references

World Health Organization

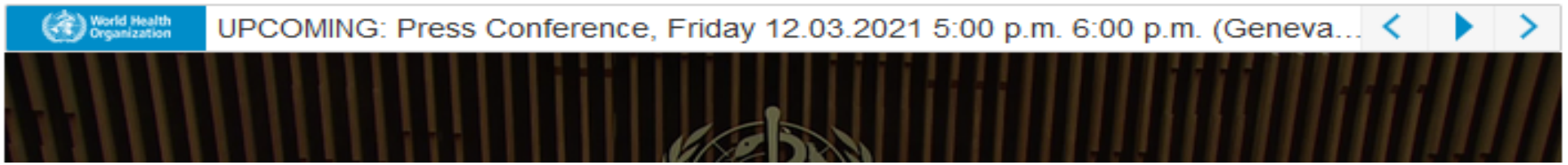
Health Topics | Countries | Newsroom | Emergencies

Home / Emergencies / Diseases / Coronavirus disease (COVID-19)

Coronavirus disease (COVID-19) pandemic

COVID-19 vaccines

Country and technical guidance



Centers for Disease Control and Prevention
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COVID-19

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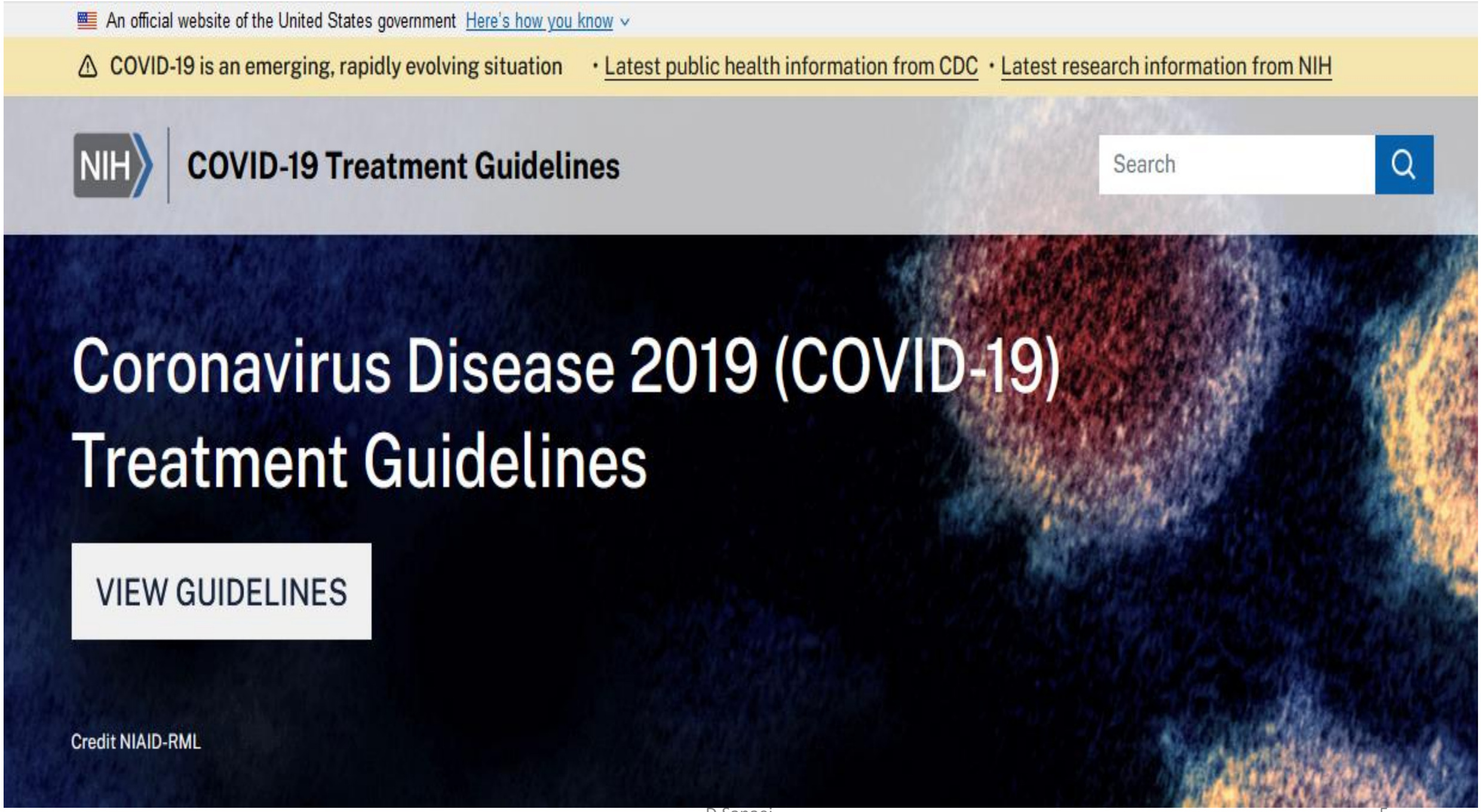
When you've been fully vaccinated

People who are fully vaccinated can start to do some things they stopped doing because of the pandemic.

Highlights

- Interim Recommendations for Fully Vaccina People
- Science Brief: Recommendations for Fully Vaccinated People
- Vaccines for Teachers & School Staff
- Variants

GUIDANCE


An official website of the United States government Here's how you know
COVID-19 is an emerging, rapidly evolving situation • Latest public health information from CDC • Latest research information from NIH
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IVAC WEBINAR

AVOIDING BARRIERS TO ACCESS FOR A COVID-19 VACCINE

September 16th, 2020

Featuring

Jerome Kim, MD
Director General, International Vaccine Institute

Naor Bar-Zeev, PhD
Deputy Director, International Vaccine Access Center

International Vaccine Institute

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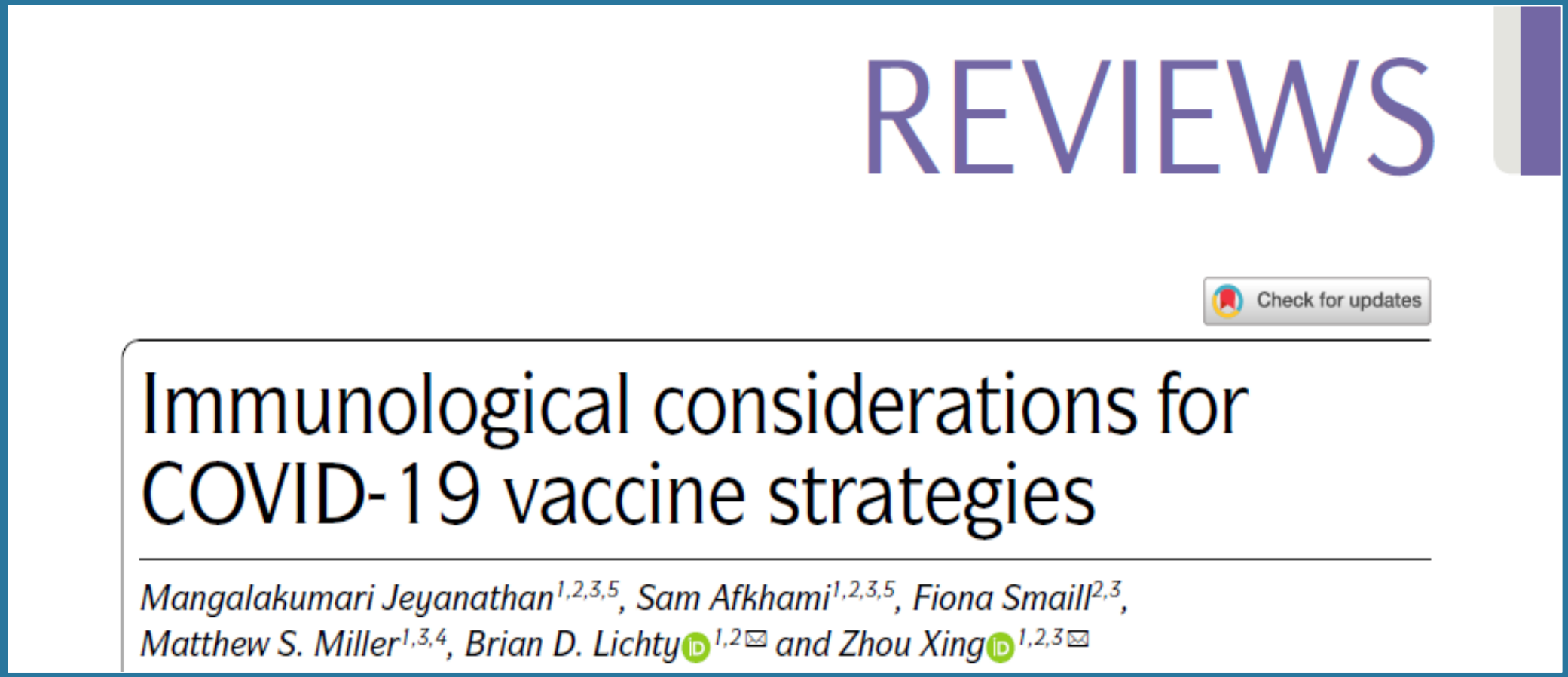
COVID-19 Vaccines

Pipeline Update

Nature Reviews | Immunology



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COVID-19 vaccines: knowing the unknown

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[2]Department of Integrative Structural and Computational Biology, The Scripps Research Institute, La Jolla, CA 92037, USA

Contents lists available at ScienceDirect

Paediatric Respiratory Reviews

Review

Vaccines for COVID-19: The current state of play

Archana Koirala [a,b], Ye Jin Joo [a], Ameneh Khatami [c,d], Clayton Chiu [a,c], Philip N. Britton [c,d,*]

[a] National Centre for Immunisation Research and Surveillance, Westmead, NSW, Australia
[b] Department of Infectious Diseases, Nepean Hospital, Penrith, NSW, Australia
[c] Sydney Medical School, The University of Sydney, NSW, Australia
[d] Department of Infectious Diseases and Microbiology, The Children's Hospital at Westmead, NSW, Australia

Educational aims

The reader will be able to:

- Understand of the types of vaccine and vaccine platforms being developed for SARS-CoV-2.
- Develop knowledge regarding the concerns around coronavirus vaccine development.
- Appreciated the issues of rapid vaccine development in outbreak settings.

frontiers in Immunology

REVIEW
published: 14 October 2020
doi: 10.3389/fimmu.2020.585354

Check for updates

A Review of the Progress and Challenges of Developing a Vaccine for COVID-19

Omna Sharma[1]*, *Ali A. Sultan*[2], *Hong Ding*[3] and *Chris R. Triggle*[3]*

[1] Weill Cornell Medicine-Qatar, Doha, Qatar, [2] Department of Microbiology and Immunology, Weill Cornell Medicine-Qatar, Cornell University, Doha, Qatar, [3] Departments of Medical Education and Pharmacology, Weill Cornell Medicine-Qatar, Education City, Doha, Qatar

nature microbiology

PERSPECTIVE

Antibody-dependent enhancement and SARS-CoV-2 vaccines and therapies

Wen Shi Lee, Adam K. Wheatley, Stephen J. Kent and Brandon J. DeKosky

European Journal of Pharmacology 892 (2021) 173751

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Review

COVID-19 vaccine: A recent update in pipeline vaccines, their design and development strategies

Kajal Rawat, Puja Kumari, Lekha Saha *

Department of Pharmacology, Post Graduate Institute of Medical Education & Research (PGIMER), 4th Floor, Research Block B, Chandigarh, 160012, India

Iran J Public Health, Vol. 49, Suppl.1, 2020, pp.18-29

Review Article

Frontier Therapeutics and Vaccine Strategies for SARS-CoV-2 (COVID-19): A Review

*Amirhossein SHEIKHSHAHROKH [1], *Reza RANJBAR [2], Elnaz SAEIDI [1], Farhad SA-FARPOOR DEHKORDI [3], Mohammad HEIAT [4], Payam GHASEMI-DEHKORDI [5], Hamed GOODARZI [2]*

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5. *Cellular and Molecular Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran*

Vaccine Research

ISSN: 2423-4923
eISSN: 2383-2819

Prospective on Different Approaches for Vaccine Development Against COVID-19: Past Lessons and Future Challenges

Rahimi Pooneh[1, 2], Aghasadeghi Mohammd Reza[1, 2]

[1]Department of Hepatitis and AIDS, Pasteur Institute of Iran, Tehran, Iran. [2]Viral Vaccine Research Center (VVRC), Pasteur Institute of Iran, Tehran, Iran

Li et al. J Biomed Sci (2020) 27:104
https://doi.org/10.1186/s12929-020-00695-2

Journal of Biomedical Science

REVIEW

Open Access

Coronavirus vaccine development: from SARS and MERS to COVID-19

Yen-Der Li[1†], Wei-Yu Chi[2†], Jun-Han Su[1], Louise Ferrall[3], Chien-Fu Hung[3] and T.-C. Wu[2,3*]

frontiers in Immunology

REVIEW
published: 23 December 2020
doi: 10.3389/fimmu.2020.602256

Check for updates

COVID-19: Coronavirus Vaccine Development Updates

Jing Zhao[1†], *Shan Zhao*[1†], *Junxian Ou*[1], *Jing Zhang*[2], *Wendong Lan*[1], *Wenyi Guan*[1], *Xiaowei Wu*[1], *Yuqian Yan*[1], *Wei Zhao*[1], *Jianguo Wu*[2], *James Chodosh*[3] and *Qiwei Zhang*[1,2*]

This is a review article submitted to the Toxicologic Pathology Forum. It represents the views of the authors. It does not constitute an official position of the Society of Toxicologic Pathology, British Society of Toxicological Pathology, or European Society of Toxicologic Pathology, and the views expressed might not reflect the best practices recommended by these Societies. This article should not be construed to represent the policies, positions, or opinions of their respective organizations, employers, or regulatory agencies.

Toxicologic Pathology
2020, Vol. 48(7) 800-809

DOI: 10.1177/0192623320959090
journals.sagepub.com/home/tpx
SAGE

Review of Current Vaccine Development Strategies to Prevent Coronavirus Disease 2019 (COVID-19)

Bindu M. Bennet[1], Jayanthi Wolf[2], Rodrigo Laureano[3], and Rani S. Sellers[4]

- Patients may have abnormalities on chest imaging before the onset of symptoms.

Monitor for Severe

- Clinicians should be aware of the potential for some patients to rapidly deteriorate 1 week after illness onset.
- The median time to acute respiratory distress syndrome (ARDS) ranges from 8 to 12 days.

Patients with moderate illness may not require emergency interventions or hospitalization; however, isolation is necessary for all suspect or confirmed cases.

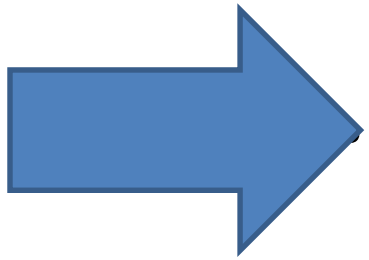
World Health Organization

Reinfection

- Reinfection with a SARS-CoV-2 variant virus has been reported
- The risk of reinfection may be increased in the future with exposure to SARS-CoV-2 variant virus strains that are not neutralized by immune antisera, such as one recently described in South Africa.

• Prolonged Detection of SARS-CoV-2

- SARS-CoV-2 RNA shedding may continue for days to weeks
- Thus, detection of viral RNA during convalescence does not necessarily indicate replication-competent virus (infectiousness) or the presence of new infectious virus.
- Some people : detectable SARS-CoV-2 RNA : up to 3 months after illness .



Some people with **severe illness** might produce replication-competent virus beyond 10 days that may warrant extending duration of isolation and precautions for up to 20 days after symptom onset.

- Limited data suggest that some **severely immunocompromised patients** (e.g., patients might produce replication-competent virus **beyond 20 days** .

who

12. Antivirals, immunomodulators and other adjunctive therapies for COVID-19

We recommend that the following drugs not be administered as treatment or prophylaxis for COVID-19, outside of the context of clinical trials:

- Chloroquine and hydroxychloroquine (+/- azithromycin), including but not limited to:
- Antivirals, including but not limited to:
  - Lopinavir/ritonavir
  - Remdesivir
  - Umifenovir
  - Favipiravir
- Immunomodulators, including but not limited to:
  - Tocilizumab
  - Interferon-β-1a
- Plasma therapy.

World Health Organization

Dexamethasone

Considerations in Children

Dexamethasone may be beneficial in pediatric patients with COVID-19 respiratory disease who require mechanical ventilation.

dexamethasone is generally not recommended for pediatric patients who require only low levels of oxygen support (i.e., nasal cannula only).

Dexamethasone	**Dose for COVID-19:** • Dexamethasone ( ) IV or PO once daily, for up to 10 days or until hospital discharge, whichever comes first[1]

Corticosteroids (IV/PO)

- *Dexamethasone-Preferred*
- Alternatives:
  - Breastfeeding/Pregnant: Prednisolone or methylprednisolone
  - Preterm infant: Corrected GA < 40 weeks: Hydrocortisone

Should only be used in patients with:

a) Respiratory support: oxygen or invasive mechanical ventilation
b) Continuation for underlying condition requiring chronic steroid treatment
c) Additional diagnosis where steroid therapy is appropriate

Preferred Drug	Dose [33-34]
Dexamethasone	0.15mg/kg once daily (Max: 6 mg)
Alternative Drugs	**Dose [33-34]**
Prednisolone	1 mg/kg once daily (Max: 40 mg)
Methylprednisolone	0.8 mg/kg once daily (Max: 32 mg)
Hydrocortisone	0.5 mg/kg q12h X 7 days 0.5 mg/kg daily X 3 days

Duration: up to 10 days

Adverse events:

- Hypertension
- Hyperglycemia

Antiviral Drugs That Are Approved or Under Evaluation for the Treatment of COVID-19

Last Updated: February 11, 2021

Summary Recommendations

Remdesivir is the only Food and Drug Administration-approved drug for the treatment of COVID-19. In this section, the COVID-19 Treatment Guidelines Panel (the Panel) provides recommendations for using antiviral drugs to treat COVID-19 based on the available data. **As in the management of any disease, treatment decisions ultimately reside with the patient and their health care provider.** For more information on these antiviral agents, see Table 2d.

Remdesivir

- See Therapeutic Management of Patients with COVID-19 for recommendations on using remdesivir with or without dexamethasone.

Chloroquine or Hydroxychloroquine With or Without Azithromycin

- The Panel **recommends against** the use of **chloroquine** or **hydroxychloroquine** with or without **azithromycin** for the treatment of COVID-19 in hospitalized patients **(AI)**.
- In nonhospitalized patients, the Panel **recommends against** the use of **chloroquine** or **hydroxychloroquine** with or without **azithromycin** for the treatment of COVID-19, except in a clinical trial **(AIIa)**.
- The Panel **recommends against** the use of **high-dose chloroquine** (600 mg twice daily for 10 days) for the treatment of COVID-19 **(AI)**.

Lopinavir/Ritonavir and Other HIV Protease Inhibitors

- The Panel **recommends against** the use of **lopinavir/ritonavir** and **other HIV protease inhibitors** for the treatment of COVID-19 in hospitalized patients **(AI)**.
- The Panel **recommends against** the use of **lopinavir/ritonavir** and **other HIV protease inhibitors** for the treatment of COVID-19 in nonhospitalized patients **(AIII)**.

Ivermectin

- There are insufficient data for the Panel to recommend either for or against the use of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin in the treatment of COVID-19.

CDC

- Only FDA Approved Drug
- Remdesivir

Remdesivir : in the first days of admission

Recommendations

Based on the collective evidence from the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) and Randomized Evaluation of COVID-19 Therapy (RECOVERY) trials, the COVID-19 Treatment Guidelines Panel (the Panel) has determined the following:

- The Panel recommends the use of **tocilizumab**[a] (single intravenous dose of 8 mg/kg of actual body weight, up to 800 mg) **in combination with dexamethasone** (6 mg daily for up to 10 days)[b] in certain hospitalized patients who are exhibiting rapid respiratory decompensation due to COVID-19.[c] The patients included in this population are:
  - Recently hospitalized patients[d] who have been admitted to the intensive care unit (ICU) within the prior 24 hours and who require invasive mechanical ventilation, noninvasive mechanical ventilation (NIV), or high-flow nasal canula (HFNC) oxygen (>0.4 FiO_2/30 L/min of oxygen flow) **(BIIa)**; *or*
  - Recently hospitalized patients[d] (not in the ICU) with rapidly increasing oxygen needs who require NIV or HFNC and have significantly increased markers of inflammation **(BIIa)** (**Note:** The RECOVERY trial inclusion criterion for inflammation was C-reactive protein [CRP] ≥75 mg/L; see details below).
- For hospitalized patients with hypoxemia who require conventional oxygen supplementation, the Panel recommends using one of the following options: **remdesivir (BIIa)**, **dexamethasone plus remdesivir (BIII)**, or **dexamethasone alone (BI)** (see Therapeutic Management of Adults With COVID-19).
  - There is insufficient evidence to specify which of these patients would benefit from the addition of tocilizumab. Some Panel members would also give tocilizumab to patients who are exhibiting rapidly increasing oxygen needs while on dexamethasone and have a CRP ≥75 mg/L but who do not yet require NIV or HFNC, as described above.

[a] Use of tocilizumab **should be avoided** in patients with any of the following: (1) significant immunosuppression, particularly in those with a history of recent use of other biologic immunomodulating drugs; (2) alanine transaminase >5 times the upper limit of normal; (3) high risk for gastrointestinal perforation; (4) an uncontrolled, serious bacterial, fungal, or non-SARS-CoV-2 viral infection; (5) absolute neutrophil count <500 cells/mL; or (6) platelet count <50,000 cells/mL.

Kinase Inhibitors

: Baricitinib and Other Janus Kinase Inhibitors, and Bruton's Tyrosine Kinase Inhibitors
Last Updated: February 11, 2021

they can prevent phosphorylation of key proteins involved in the signal transduction that leads to immune activation and inflammation (e.g., the cellular response to proinflammatory cytokines such as interleukin [IL]-6).

Janus kinase (JAK) inhibitors interfere with phosphorylation of signal transducer and activator of transcription (STAT) proteins2,3 that are involved in vital cellular functions, including signaling, growth, and survival.
Immunosuppression induced by this class of drugs could potentially reduce the inflammation and associated immunopathologies observed in patients with COVID-19.
Additionally, JAK inhibitors, particularly baricitinib, have theoretical direct antiviral activity through interference with viral endocytosis, potentially preventing entry into and infection of susceptible cells.
Recommendations• There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized patients, when corticosteroids can be used.•
In the rare circumstance when corticosteroids cannot be used, the Panel recommends baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized, non-intubated patients who require oxygen supplementation (BIIa).• The Panel recommends against the use of baricitinib without remdesivir, except in a clinical trial (AIII).• There are insufficient data for the Panel to recommend either for or against the use of baricitinib in combination with corticosteroids for the treatment of COVID-19. Because both baricitinib and corticosteroids are potent immunosuppressants, there is potential for an additive risk of infection.• The Panel recommends against the use of JAK inhibitors other than baricitinib for the treatment of COVID-19, except in a clinical trial (AIII).

Considerations in Children

EUA : use of baricitinib in combination with remdesivir in hospitalized adults and children aged ≥2 years with COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or ECMO.

Thus, there are insufficient data to recommend either for or against the use of baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized children when corticosteroids cannot be used.

Use of JAK inhibitors other than baricitinib for the treatment of COVID-19 in pediatric patients is not recommended, except in a clinical trial

Anakinra

- Last Updated: July 17,
- There are insufficient data to recommend for or against the use of interleukin (IL)-1 inhibitors, such as anakinra, for the treatment of COVID-19

COVID-19-associated coagulopathy :

- Mild thrombocytopenia
- Increased D-dimer levels
- Increased fibrin degradation products
- Prolonged prothrombin time
- Elevated D-dimer levels have been strongly associated with greater risk of death
- deep venous thrombosis
- pulmonary embolism
- Microvascular thrombosis of the toes (“COVID toes”)
- Clotting of intra-vascular catheters
- Myocardial injury with ST-segment elevation
- Large vessel strokes

Summary Recommendations

Laboratory Testing

- In nonhospitalized patients with COVID-19, there are currently no data to support the measurement of coagulation markers (e.g., D-dimers, prothrombin time, platelet count, fibrinogen) **(AIII)**.
- In hospitalized patients with COVID-19, hematologic and coagulation parameters are commonly measured, although there are currently insufficient data to recommend either for or against using this data to guide management decisions.

Chronic Anticoagulant and Antiplatelet Therapy

- Patients who are receiving anticoagulant or antiplatelet therapies for underlying conditions should continue these medications if they receive a diagnosis of COVID-19 **(AIII)**.

Venous Thromboembolism Prophylaxis and Screening

- For nonhospitalized patients with COVID-19, anticoagulants and antiplatelet therapy should not be initiated for the prevention of venous thromboembolism (VTE) or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial **(AIII)**.
- Hospitalized nonpregnant adults with COVID-19 should receive prophylactic dose anticoagulation **(AIII)** (see the recommendations for pregnant individuals below). Anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the usual standard of care for patients without COVID-19 **(AIII)**.
- There are currently insufficient data to recommend either for or against the use of thrombolytics or higher than the prophylactic dose of anticoagulation for VTE prophylaxis in hospitalized COVID-19 patients outside of a clinical trial.
- Hospitalized patients with COVID-19 should not routinely be discharged from the hospital while on VTE prophylaxis **(AIII)**. Continuing anticoagulation with a Food and Drug Administration-approved regimen for extended VTE prophylaxis after hospital discharge can be considered for patients who are at low risk for bleeding and high risk for VTE, as per the protocols for patients without COVID-19 (see details on defining at-risk patients below) **(BI)**.
- There are currently insufficient data to recommend either for or against routine deep vein thrombosis screening in COVID-19 patients without signs or symptoms of VTE, regardless of the status of their coagulation markers.
- For hospitalized COVID-19 patients who experience rapid deterioration of pulmonary, cardiac, or neurological function, or of sudden, localized loss of peripheral perfusion, the possibility of thromboembolic disease should be evaluated **(AIII)**.

Hospitalized Children With COVID-19

- For hospitalized children with COVID-19, indications for VTE prophylaxis should be the same as those for children without COVID-19 **(BIII)**.

Important

Hospitalized Children With COVID-19

- For hospitalized children with COVID-19, indications for VTE prophylaxis should be the same as those for children without COVID-19 **(BIII)**.

- Hospitalized Children With COVID-19

- VTE prophylaxis after hospital discharge is not recommended for patients with COVID-19
- For certain high-VTE risk patients without COVID-19, post-discharge prophylaxis has been shown to be beneficial.
- decision to use post-discharge VTE prophylaxis : consideration of patient’s risk factors for VTE, including reduced mobility, bleeding risks, and feasibility. Participation in clinical trials is encouraged

Monitoring Coagulation Markers in Patients With COVID-19

Nonhospitalized patients with COVID-19, markers of coagulopathy, such as D-dimer level, prothrombin time, fibrinogen level, and platelet count, should not routinely be obtained and anticoagulants and antiplatelet therapy should not be initiated for the prevention of VTE or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial

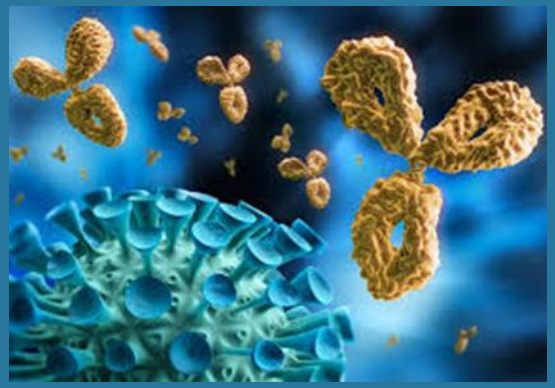
Prevention and Prophylaxis of SARS-CoV-2 Infection

Last Updated: February 11, 2021

Summary Recommendations
• The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of any drugs for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pre-exposure prophylaxis (PrEP), except in a clinical trial **(AIII)**. • The Panel **recommends against** the use of **hydroxychloroquine** for SARS-CoV-2 post-exposure prophylaxis (PEP) **(AI)**. • The Panel **recommends against** the use of other drugs for SARS-CoV-2 PEP, except in a clinical trial **(AIII)**. • The Panel recommends that health care providers follow recommendations from the Advisory Committee on Immunization Practices when using SARS-CoV-2 vaccines **(AI)**..
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

In the name of God

COVID 19 VACCINES



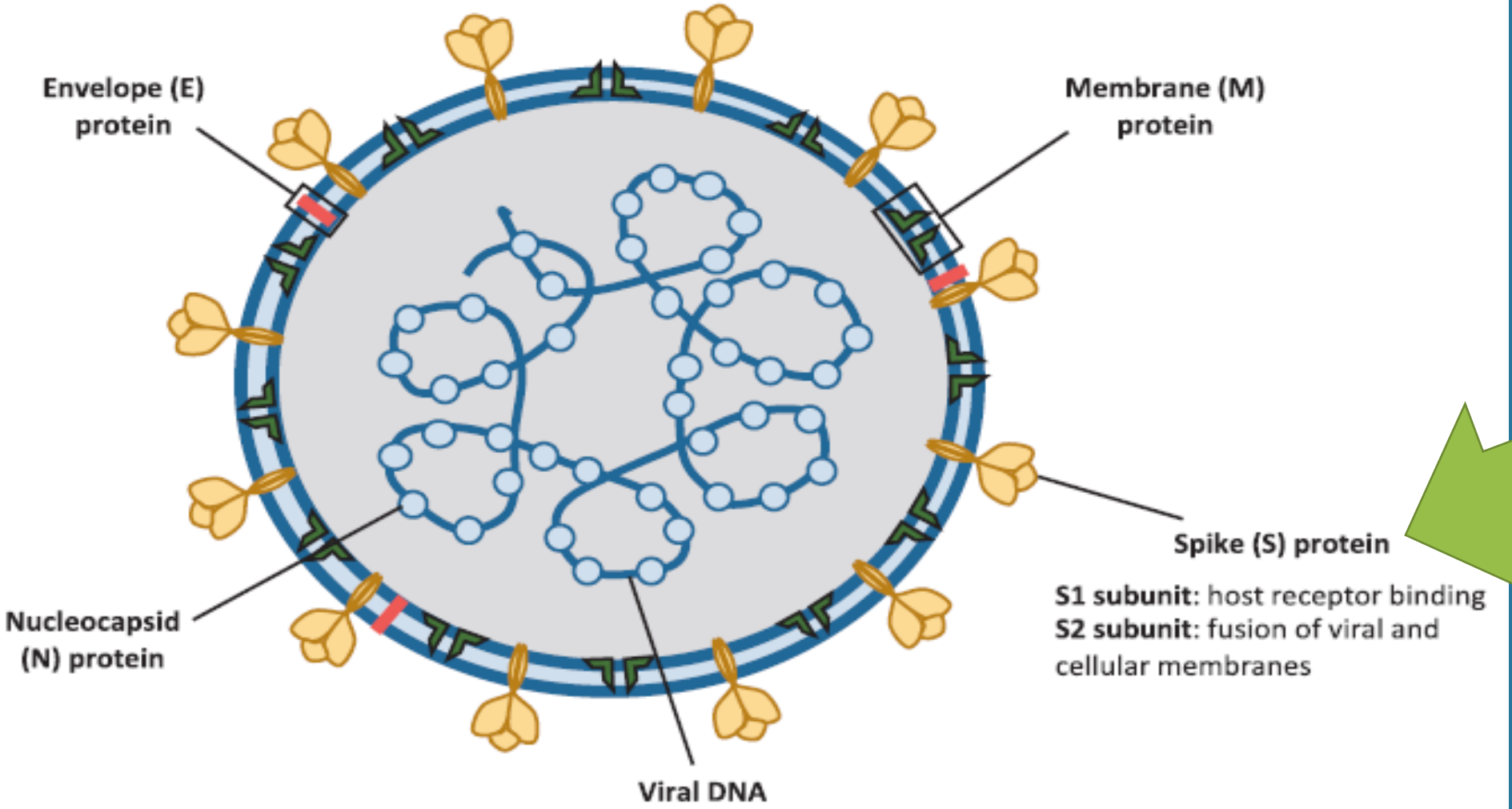


Fig. 1. Schematic of the structure of SARS-CoV2. *(Adapted from Lee, C-Y et al, Frontiers in Immunology, 2020)* [100].

Archana Koirala

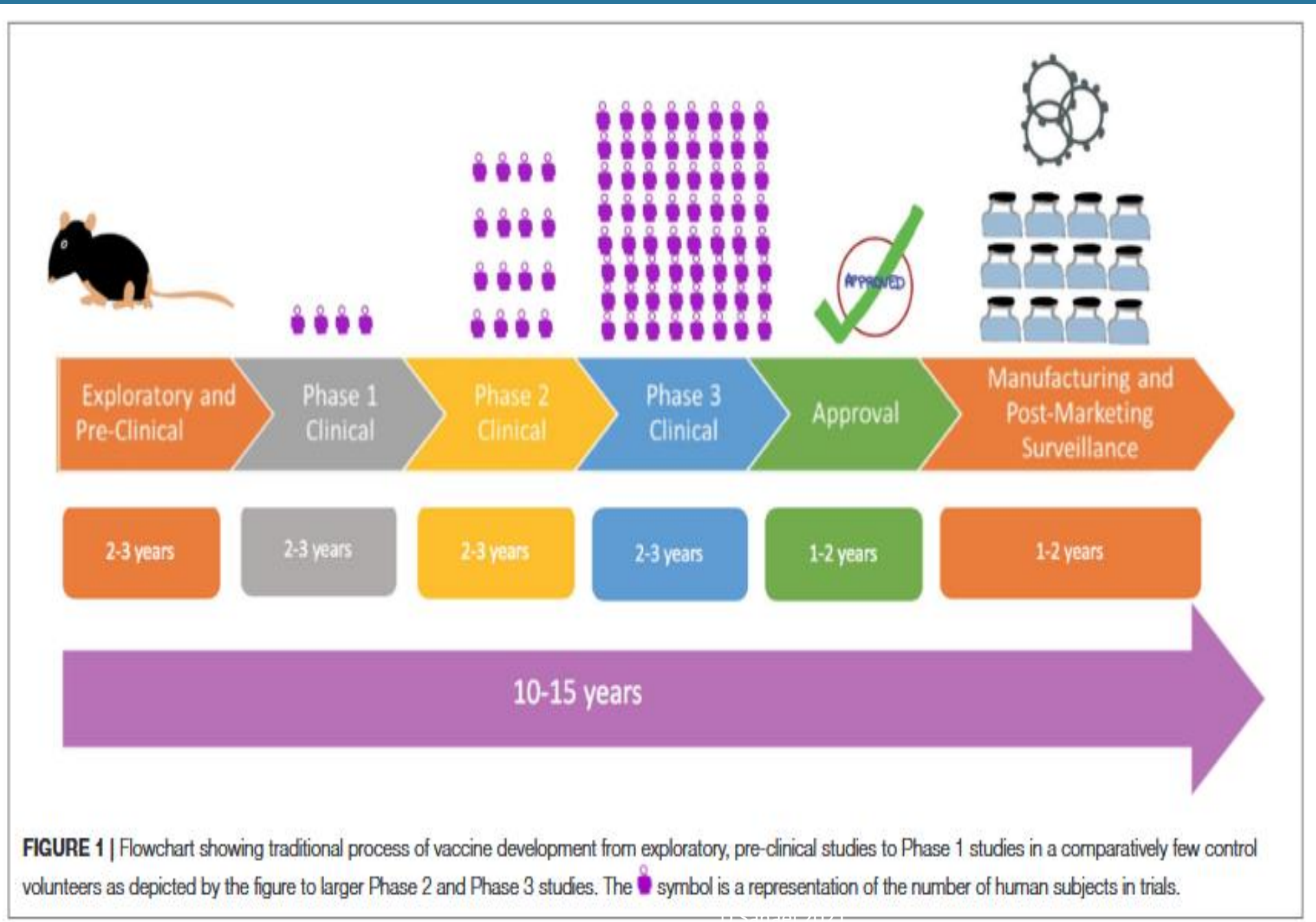


FIGURE 1 | Flowchart showing traditional process of vaccine development from exploratory, pre-clinical studies to Phase 1 studies in a comparatively few control volunteers as depicted by the figure to larger Phase 2 and Phase 3 studies. The symbol is a representation of the number of human subjects in trials.

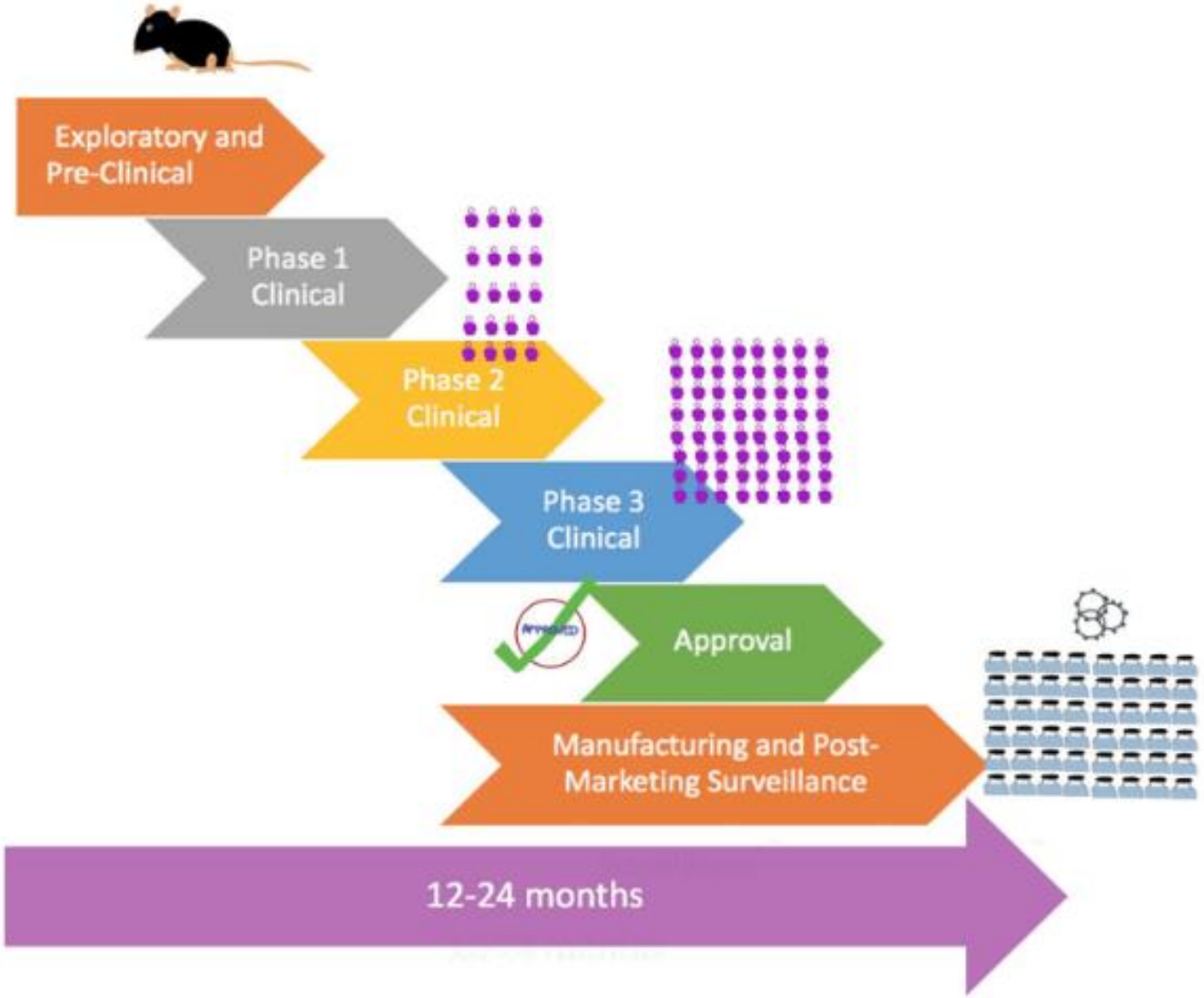
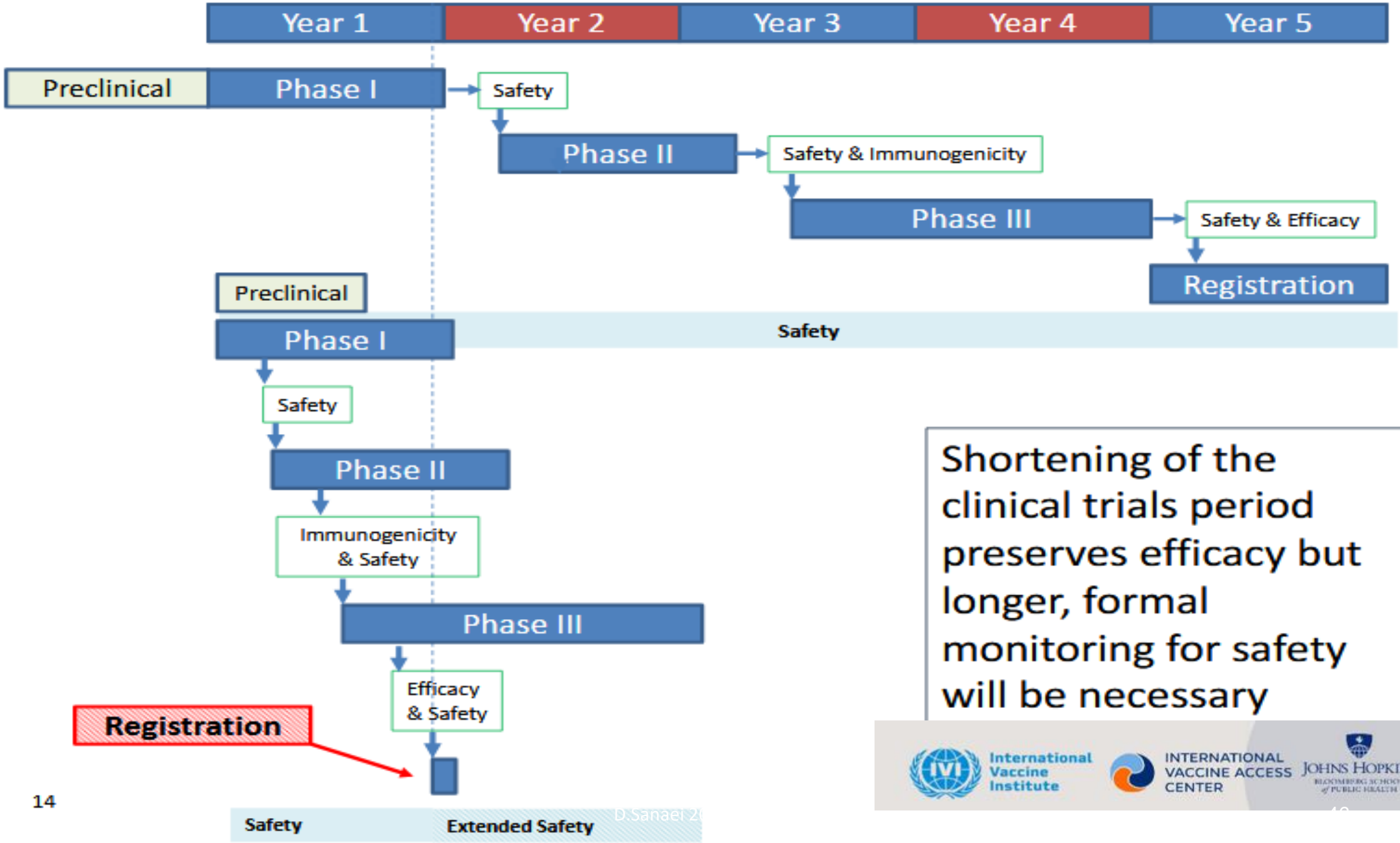


FIGURE 2 | Flowchart showing accelerated process of vaccine development in a pandemic with combined phases, pre-approval, and rapid large-scale manufacturing. The symbol is a representation of the number of human subjects in trials.



Shortening of the clinical trials period preserves efficacy but longer, formal monitoring for safety will be necessary

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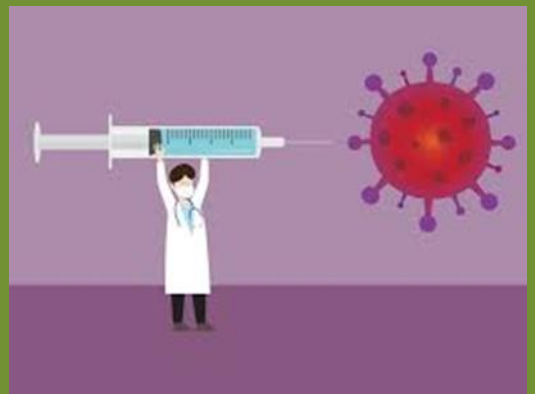
Emergency Use Authorization (EUA)

An **Emergency Use Authorization** (**EUA**) in the United States is an authorization granted to the Food and Drug Administration (FDA) to allow the use of a drug prior to approval during a declared state of emergency

- Pfizer .
- Moderna

Jansen



COVID-19 vaccine candidates in Phase III trials

- As of 16 December 2020 there are **56 COVID-19 candidate vaccines** in clinical evaluation of which **13 are in Phase III trials**
- There are another **166 candidate vaccines in preclinical** evaluation
- Phase III trials usually require **30,000 or more participants**
- All top candidate vaccines will be delivered through **intra-muscular** injection
- Most are designed for a **two-dose** schedule (exceptions with a * in table are single dose)

Source:
https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

13 CANIDATE VACCINES IN PHASE III CLINICAL EVALUATION	VACCINE PLATFORM	LOCATION OF PHASE III STUDIES
Sinovac	Inactivated virus	Brazil
Wuhan Institute of Biological Products / Sinopharm	Inactivated virus	United Arab Emirates
Beijing Institute of Biological Products / Sinopharm	Inactivated virus	China
Bharat Biotech	Inactivated virus	India
University of Oxford / AstraZeneca	Viral vector	USA
CanSino Biological Inc. / Beijing Institute of Biotechnology	Viral vector *	Pakistan
Gamaleya Research Institute	Viral vector	Russia
Janssen Pharmaceutical Companies	Viral vector	USA, Brazil, Colombia, Peru, Mexico, Philippines, South Africa
Novavax	Protein subunit	The United Kingdom
Anhui Zhifei Longcom Biopharma/ Institute of Microbiology, Chinese Academy of Sciences	Protein subunit	China
Moderna / NIAID	RNA	USA
BioNTech / Fosun Pharma / Pfizer	RNA	USA, Argentina, Brazil
Medicago Inc	VLP	Canada

* Single dose schedule

Vaccine candidates

from age 18 years to 50 to 60 years.

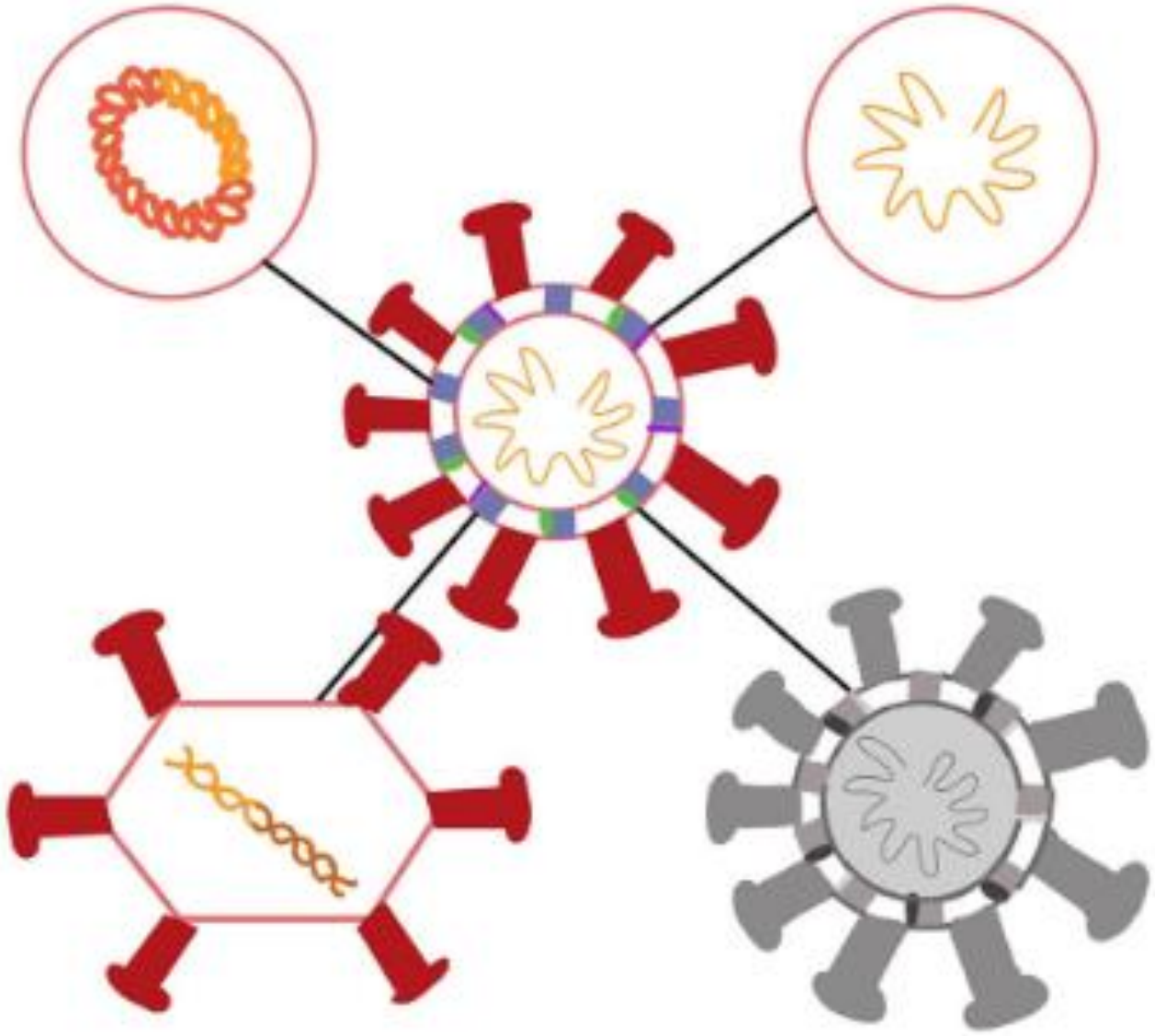
- Two trials in aged 3 years and 6 years.

DNA

- Inovio Pharmaceuticals

RNA

- Moderna/NIAID
- BionTech/Fosun/ Pfizer



Viral vector

- AstraZeneca/Oxford
- CanSino Biological Inc./Beijing Institute of Biotechnology

Inactivated

- Wuhan Institute of Biological Products/Sinopharm
- Beijing Institute of Biological Products/Sinopharm
- Sinovac

Nucleic acid vaccines: DNA,RNA

- Nucleic acid vaccines utilize antigen-encoding plasmid DNA or RNA, messenger RNA (mRNA) or viral replicons.
- The nucleic acid, once taken up by a cell will initiate protein synthesis, to which a humoral and cell-mediated immune response is expected to occur, similar to natural infection.
- Example: foot and mouth disease, deer powassan virus and rabies virus

- The benefit of a nucleic acid platform is
- the ease with which it allows antigen manipulation and
- the speed of production, as manufacturing can be synthetic and entirely cell free so no need for BSL2 laboratories.
- The disadvantages :
- nucleic acid, especially mRNA, are fragile and require a uninterrupted cold-chain process for transport and storage

Archana Koirala

DNA-based vaccines work by inserting synthetic DNA of viral gene(s) into small DNA molecules (called plasmids). Cells take in the DNA plasmids and follow their instructions to build viral proteins, which are recognized by the immune system, and prepare it to respond to disease exposure

Platform	Description	Advantages	Disadvantages
DNA	DNA that encodes the target antigen **INO-4800** Phase I: Inovio Pharmaceuticals NCT04336410 [98] Participants : 18–50 years $n = 40$ **Plasmid DNA oral vaccine (bacTRL-IL-Spike-1)** Phase 1: Symvivo NCT04334980 [99] Participants: 19 = 55 years; $n = 84$	Easier to design Rapid manufacture	May require a special approach to administer the vaccine (e.g. electroporation device) May requires adjuvant Uncertainty of safety issues

S protein	Unimpeded owing to lack of pre-existing antivector immunity	T_H1 cell

Response not as strong as for some of the viral vectors

Parenteral (IM) in clinical trials	Weaker than mRNA-based vaccine; requires repeated delivery	Adjuvant required; not amenable to RM vaccination

D.Sanaei 2021

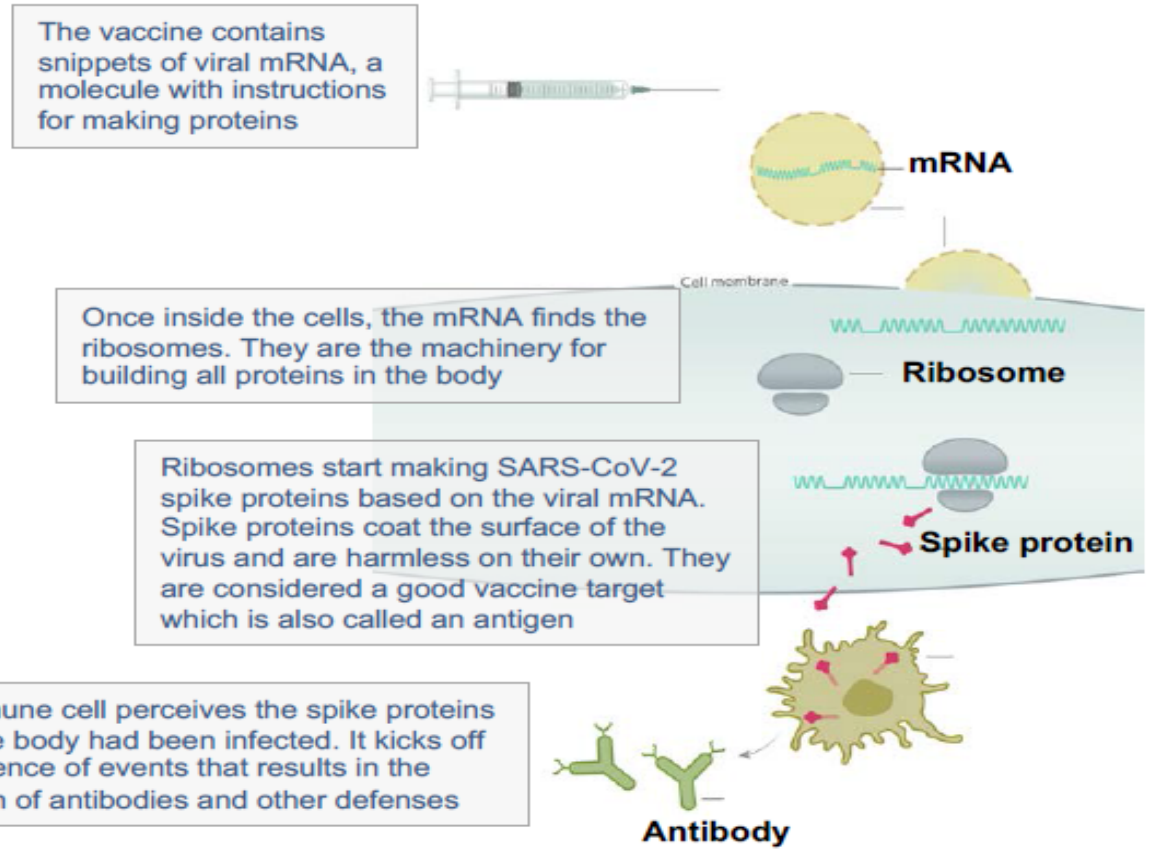
Archana Koirala

RNA vaccines introduce an mRNA sequence coded for a disease-specific antigen. Once this antigen is reproduced within the body, it is recognized and triggers an immune response

How the mRNA vaccines work

Pfizer-BioNTech and Moderna are mRNA vaccines

- The traditional methods of vaccine development introduce the body to either an inactivated or weakened form of a virus or to one of its viral proteins
- Instead, **mRNA vaccines inject nucleic acid coding for the antigen**
- The development of mRNA vaccines is faster as it bypasses the more laborious tasks of inactivating viruses or isolating proteins



Source:
https://www.nationalgeographic.com/science/2020/05/moderna-coronavirus-vaccine-how-it-works-cvd/

mRNA	mRNA encoding target antigen (may be complexed with lipid- or polymer-based nanoparticles)	Easier to design Induces strong immune response Rapid manufacture	Requires mRNA to be encapsulated otherwise unstable under physiological conditions

T_H1 cell or T_H2 cell depending on adjuvant	S protein or RBD encapsulated in lipid nanoparticle	Parenteral (IM) in clinical trials	Requires repeated delivery	Adjuvant required; unclear whether it is amenable to RM vaccination

Candidate vaccines:

BNT162

Phase I/II: BioNTech/Pfizer

Four candidates, two candidates include a nucleoside modified mRNA, one a uridine containing mRNA and the fourth self- amplifying mRNA. Each combined with a lipid nanoparticle formulation.

two repeated doses of IM injection

Germany 2020–001038-36 [97]

Participants: 18–55 years; *n* = 196

USA NCT04368728 [96]

Participants: 18–85 years; *n* = 7600

mRNA-1273

Lipid nano-particle (LNP)-encapsulated mRNA vaccine;

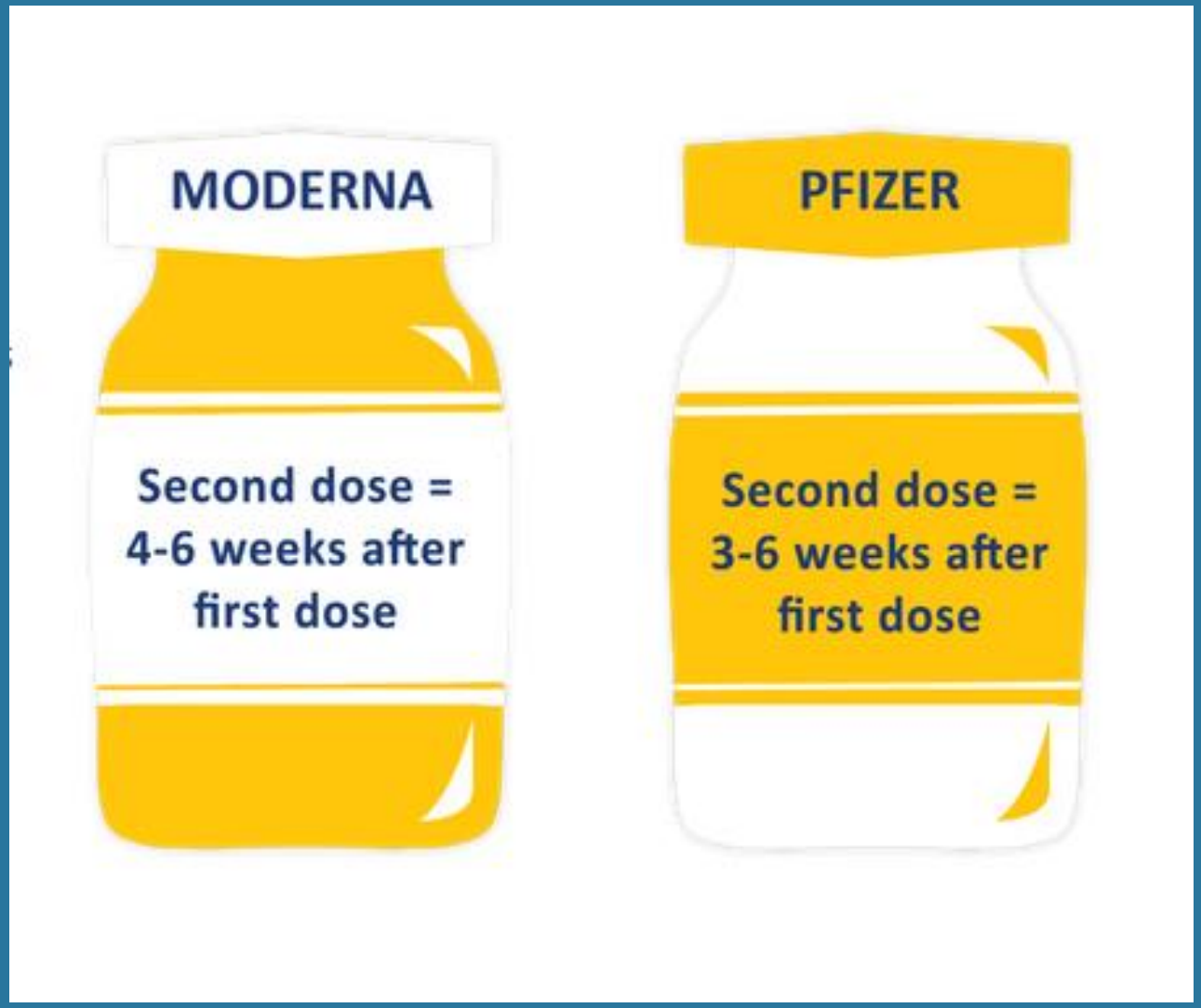
Coding antigen: full length S-protein

Phase I/II: Moderna/National Institute of Allergy and infectious diseases

NCT04283461 [59]

two repeated doses of IM injection

Archana Koirala


MODERNA
Second dose = 4-6 weeks after first dose
PFIZER
Second dose = 3-6 weeks after first dose

Inactivated vaccines consist of the whole virus, which has been killed with heat or chemicals so it can't cause illness.

sinovac

Inactivated	Wuhan Institute of Biological Products/Sinopharm - phase 3	Inactivated	Whole virus	Multiple	Medium	Mostly humoral	-Pathogen is killed and hence, no risk of reversion	-Risk of vaccine-enhanced disease -Usually produce a weak immune response
	Beijing Institute of Biological Products/Sinopharm - phase 3		Whole virus					
	Sinovac - phase 3	Inactivated + aluminum adjuvant	Whole virus			Mostly humoral - aluminum adjuvant enhances response more robust		

Omna Sharma

Viral vector technology

- Viral vector technology involves the delivery of one or more genes that encode a target antigen within an unrelated, engineered virus.
- The viral vector can be replication competent (live attenuated) or replication deficient

- Concerns with this platform :
- slower speed of vaccine manufacturing ;m the need for biosafety level 2 (BSL2) and
- possible pre-existing immunity in vaccine recipients to viral vectors such as Ad5 and MV decreasing the effectiveness of the vaccine.
- the selection of low human prevalence adenoviral serotypes (Ad26 or Ad35)
- The recombinant vesicular stomatitis virus-Zaire Ebola virus (rVSV-ZEBOV)
- Ebola vaccine is currently the only vector-vaccine that has been licensed .

Archana Koirala

Platform	Description	Advantages	Disadvantages
Recombinant Viral vector	Unrelated virus engineered to encode the target gene of the pathogen. Viral vectors can be replicating or non-replicating	Induces high cellular and humoral immune responses	Possible pre-existing immunity against vector Risk of reversion to virulence Limitations in scaling-up production

Parenteral (IM) in clinical trials	Strong with single delivery but hindered by pre-existing antivector immunity	Ample human safety data; RM delivery helps bypass antivector immunity; can be delivered by inhaled aerosol

Candidate vaccines:

Ad5-CoV

SHANGHAI, CHINA,

Adenovirus Type 5 vector; antigen: Spike protein

Phase I: CanSino Biologics ChiCTR2000030906 [88]/NCT04313127 [89]

Phase II: Institute of Biotechnology; Academy of Military Medical Sciences ChiCTR2000031781 [90]/NCT04341389 [91]

Participants: 18–60 years; Phase I *n* = 108Phase II: *n* = 508

Published data showing high dose unsafe, low and medium doses elicit neutralizing antibodies in ~50–60% of vaccinees; antibody levels negatively associated with pre-existing antivector immunity and age (>55 years)

Phase I: vaccine was safe and tolerable. No serious adverse effects. 63 participants (Low dose n = 18 [50%); moderate dose n = 18 [50%]; high dose n = 27 [75%]) developed four fold rise in neutralising antibody titres by Day 28. Pre-existing immunity to Ad5 neutralising antibody titre was observed in half of the participants before vaccination. Out of these, a low proportion seroconverted [1,76]

U.K

AZD1222 (previous known as ChAdOx1 nCoV-19)

Simian adenoviral vaccine vector; antigen: Spike protein

Phase I/II: University of Oxford NCT04324606 [92]

Participants: 18–55 years; *n* = 1090

single dose or two repeated doses of IM injection

Published data showing safety and good induction of neutralizing antibodies and T cell activation in >90% of vaccinees

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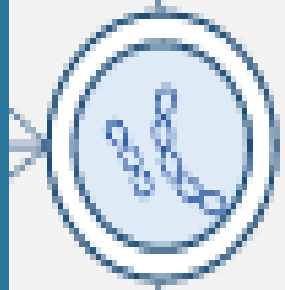
Subunit vaccines introduce a fragment of the virus into the body. This fragment is enough to be recognized by the immune response and stimulate immunity.



NOVAVAX

Clover

Protein subunit	Components of target antigen protein produced in laboratory; some vaccines may use nanoparticle technology	High safety Scalability	High cost Lower immunogenicity and may require adjuvant or repeat doses
Candidate vaccines:	**NVX-CoV2373** Phase I: Novovax NCT04368988 [96] Participants: 18–59 years; $n = 131$		

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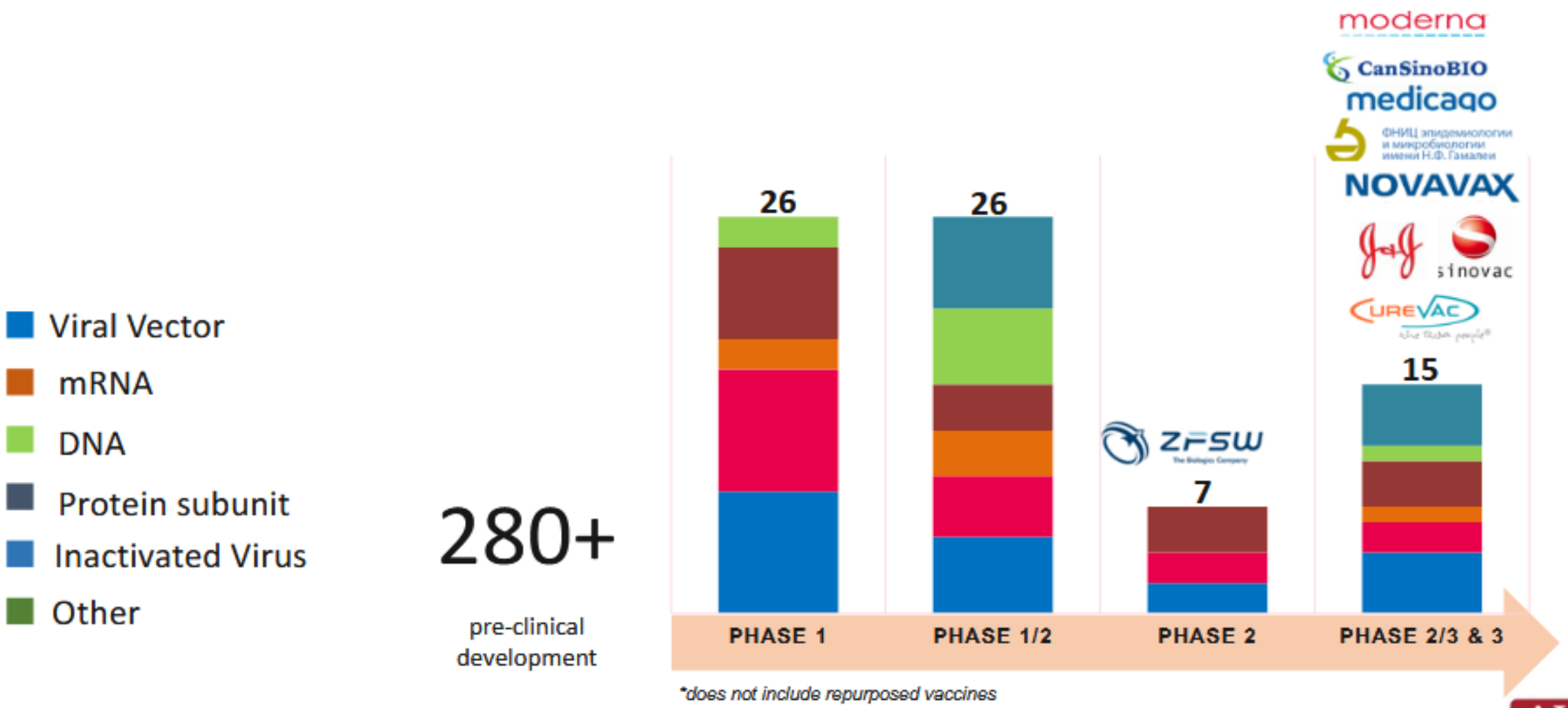
Live attenuated vaccines are made up of whole viruses that have weakened in a lab. They tend to elicit a stronger immune response than inactivated vaccines.

Live attenuated	Live virus whose genome(s) is mutated, inducing immune response but not disease	Induces long-term immunity	Expensive to produce
Candidate vaccines:	Nil in clinical trials as yet		

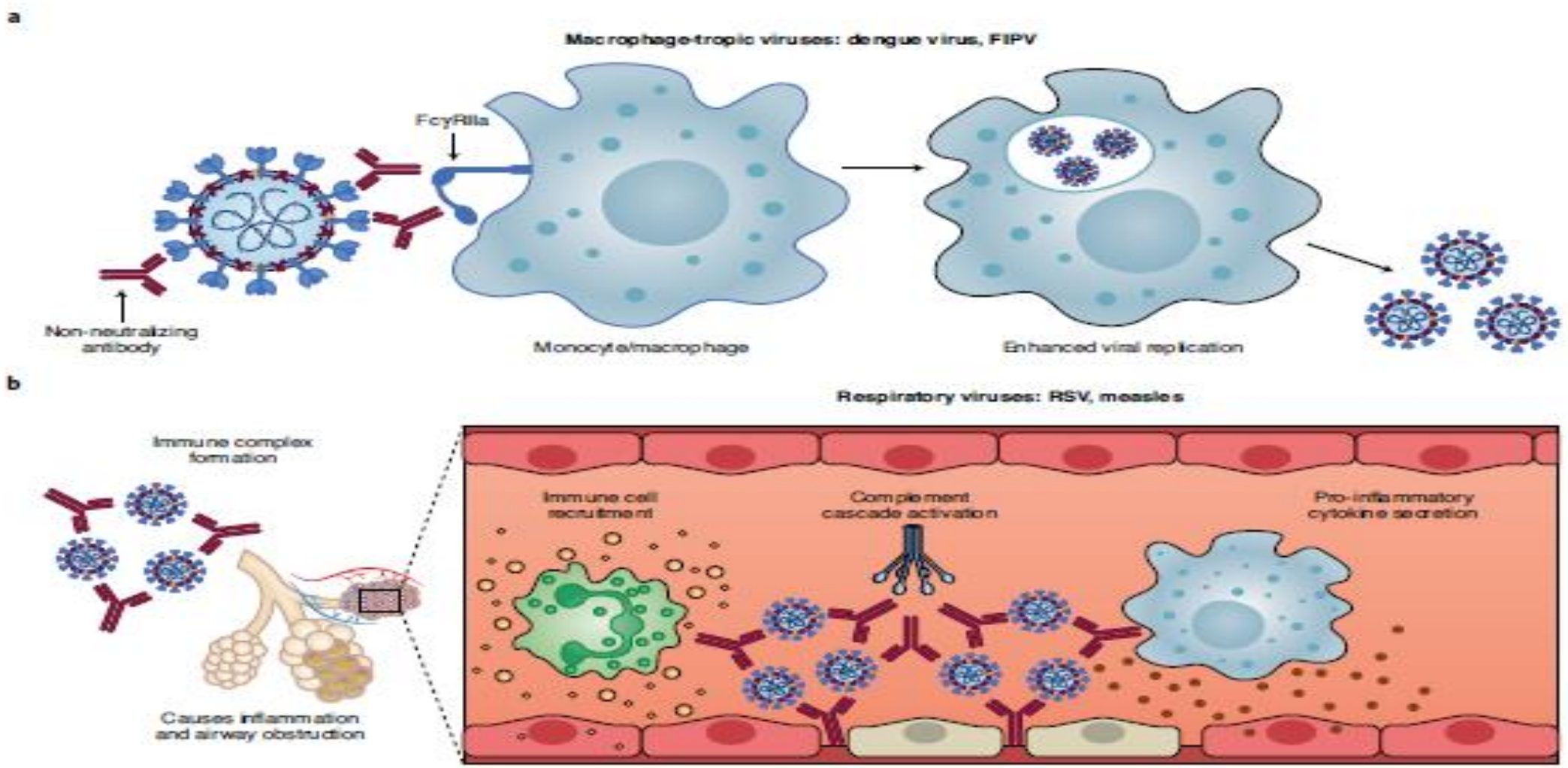
COVID Vaccine Pipeline Diversity



Antibody dependent enhancement

- **Antibody dependent enhancement** : (ADE) occur through two distinct mechanisms in viral infections:
- 1-by enhanced antibody-mediated virus uptake into Fc gamma receptor IIa (FcγRIIa)-expressing phagocytic cells leading to increased viral infection and replication, or
- 2-by excessive antibody Fc-mediated effector functions or immune complex formation causing enhanced inflammation and immunopathology
- Both ADE pathways can occur when non-neutralizing antibodies or antibodies at sub-neutralizing levels bind to viral antigens without blocking or clearing infection.

Wen shen lee


a
Macrophage-tropic viruses: dengue virus, FIPV
FcγRIIa
Non-neutralizing antibody
Monocyte/macrophage
Enhanced viral replication
b
Respiratory viruses: RSV, measles
Immune complex formation
Causes inflammation and airway obstruction
Immune cell recruitment
Complement cascade activation
Pro-inflammatory cytokine secretion

Wen shen lee

- To date, enhanced disease has not been observed with SARSCoV- 2 vaccines in preclinical models or humans.

Bindu M. Bennet

- The effect of SARS-CoV-2 Spike protein mutations is thus far uncertain, although there is no evidence that it will impact vaccine efficacy.

Bindu M. Bennet

Sputnik V

THE FIRST REGISTERED COVID-19 VACCINE

PROVEN HUMAN ADENOVIRAL VECTOR TECHNOLOGY

РУС **ENG** 中文 عربي ESP POR FRA TGL MSA

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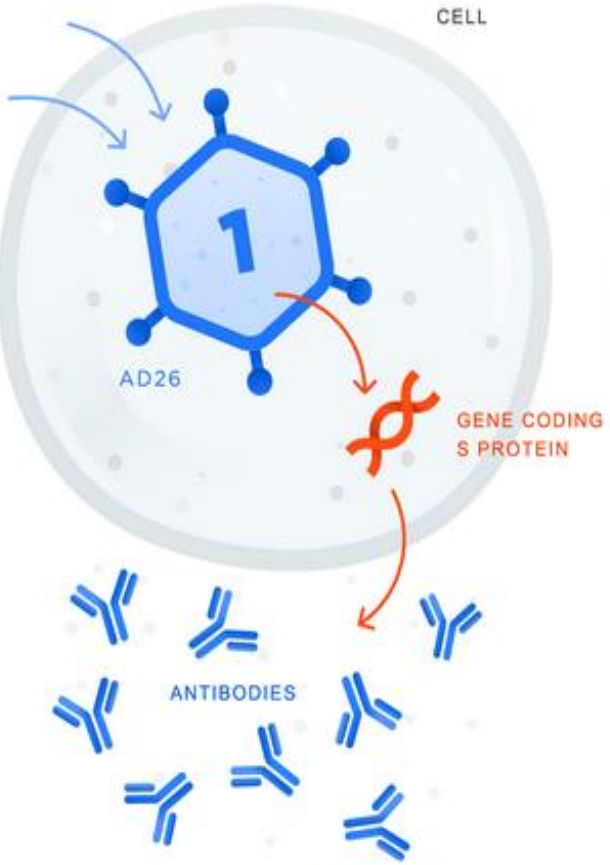
First vaccination

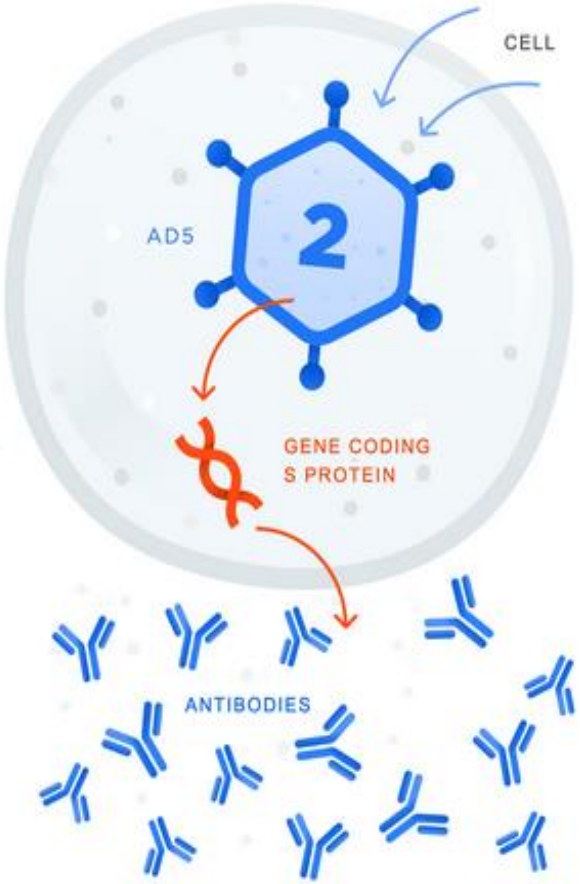
Vector with a gene coding S protein of coronavirus gets into a cell



The body synthesizes S protein, in response, the production of immunity begins

Second vaccination

Repeated vaccination takes place in 21 days



The vaccine based on another adenovirus vector unknown to the body boosts the immune response and provides for long-lasting immunity

The use of two vectors is a unique technology of the Gamaleya Center making the Russian vaccine different from other adenovirus vector-based vaccines being developed globally

Sputnik V
THE FIRST REGISTERED COVID-19 VACCINE
PROVEN HUMAN ADENOVIRAL VECTOR TECHNOLOGY

- نخستین پروژه ساخت واکسن کرونا در ایران
- «کُووایران برکت»
- توسط شرکت داروسازی شفا Shifa Pharmed
- یکی از شش پروژه ایرانی در فهرست سازمان جهانی بهداشت
- روش ساخت آن همانند دو واکسن چینی ساخت شرکت‌های «سینوفارم» و «سینوواک» است.

- شرکت دانش بنیان برکت :
- واکسن کرونا مبتنی بر پلتفرمهای ««Inactivated»، «DNA»،«Subunit»، «Recombinant»، «mRNA»، «سلول بنیادی»

- «واکسن سازی رازی» :
- مبتنی بر «پروتئین نوترکیب»
- mRNAایرانی
- «ویروس کشته شده»

واکسن مشترک پاستور و کوبا وارد فاز ۳ بالینی می‌شود

آزمایش بالینی واکسن کرونا تزریقی - استنشاقی ایرانی «رازی کوو پارس» شروع شد

جدول پروژه‌های فعال واکسن کرونای ایرانی

ردیف	مؤسسه یا شرکت	نوع واکسن مبتنی بر	فاز	مشابه واکسن کرونای خارجی
۱	ستاد اجرایی فرمان امام خمینی (ره)؛ مؤسسه برکت	ویروس کشته شده یا غیرفعال «Inactivated »	مرحله اول کارآزمایی بالینی	واکسن آکسفورد / استروزنیکا سینوواک اسپوتنیک
			در حال اخذ مجوز بالینی	-
		«DNA »	-	-
		«Subunit »	-	-
		mRNA	اتمام فاز حیوانی	واکسن فایزر / مدرنا
		سلول بنیادی	اتمام فاز حیوانی	-
۲	موسسه واکسن سازی رازی	پروتئین نوترکیب	در حال اخذ مجوز بالینی	واکسن نواوکس
۳	شرکت دانش بنیان	mRNA	در حال اخذ مجوز بالینی	فایزر / مدرنا

۴	انستیتو پاستور ایران	پروتئین نوترکیب	فاز ۳ کارآزمایی بالینی مشترک با کوبا از بهمن ماه	واکسن نواوکس
۵	شرکت دانش بنیان	«آدنو ویروس» ناقل ویروسی غیر تکثیر شونده	فاز حیوانی	از نظر نوع ویروس چین و روسیه؛ از لحاظ تکنولوژی شبیه این دو و آسترازنکا و جانسون
۶	شرکت دانش بنیان-وزارت دفاع	ویروس غیرفعال	بررسی برای اخذ مجوز بالینی	واکسن آکسفورد / استروزنیکا سینوواک اسپوتنیک
۷	شرکت دانش بنیان	ویروس غیرفعال	فاز حیوانی	واکسن آکسفورد / استروزنیکا سینوواک اسپوتنیک
۸	دانشگاه علوم پزشکی بقیه الله (عج)	پروتئین نوترکیب	فاز حیوانی	واکسن نواوکس

Comirnaty

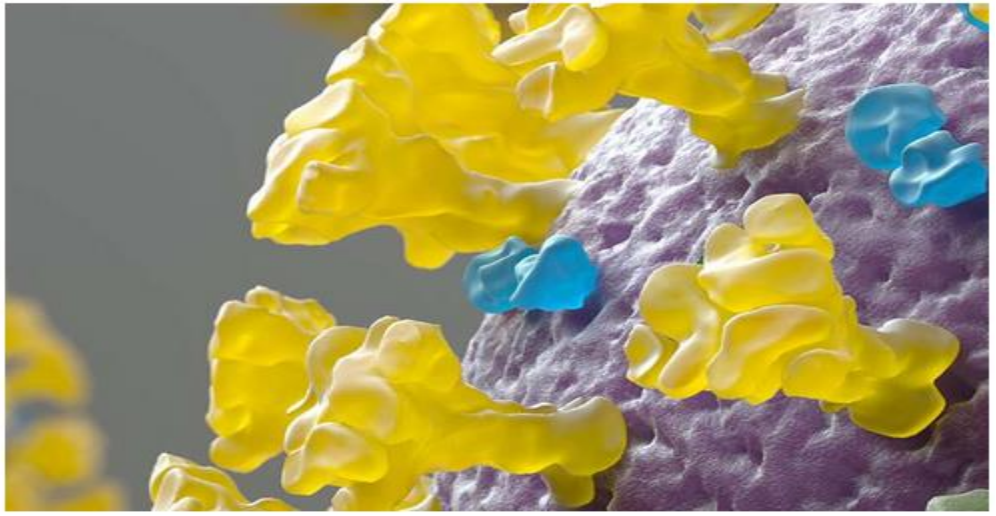
- Individuals 16 years of age and older
- It is recommended to administer the second dose 3 weeks after the first dose
- the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia)
- Shelf life Unopened vial6 months at -90 °C to -60 °C.
- Once removed from the freezer, the unopened vaccine can be stored for up to 5 days at 2 °C to 8 °C, and up to 2 hours at temperatures up to 30 °C, prior to use.
- The most frequent adverse reactions
- injection site pain(> 80%),
- fatigue (> 60%),
- headache (> 50%),
- myalgia and chills (> 30%),
- arthralgia (> 20%), pyrexia and
- injection site swelling (> 10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination.

- An immediate allergic reaction means a reaction within 4 hours of getting vaccinated: hives, swelling, or wheezing (respiratory distress).
- This includes allergic reactions to polyethylene glycol (PEG) and polysorbate.
- People who are allergic to PEG or polysorbate should not get an mRNA COVID-19 vaccine

- reactogenicity symptoms (side effects that happen within 7 days of getting vaccinated) were common but mostly mild to moderate.
- Side effects (such as fever, chills, tiredness, and headache) throughout the body were more common after the second dose of the vaccine.
- a small number of people had severe side effects: affecting a person's ability to do daily activities.

WHO

Most pregnant women shouldn’t take the Covid-19 vaccines from Moderna and Pfizer-BioNTech unless at high risk of exposure or severe illness



Russia's Sputnik V vaccine

If you have decided to join the trials, you are not recommended to **get pregnant, breastfeed the baby, and donate eggs** within three months following the vaccination .

INTERIM COVID-19 VACCINE PROVIDER GUIDE

While there is otherwise no recommended minimum interval between infection and vaccination, current evidence suggests that risk of COVID-19 reinfection is low in the months after initial infection. While vaccine supply remains limited, people who have a recent documented COVID-19 infection may choose to temporarily delay vaccination (if desired). The risk of COVID-19 infection and the need for vaccination may increase with time following initial infection due to fading immunity.

Fauci: minimum 90 days

People who previously received passive antibody therapy for COVID-19

Based on the estimated half-life of antibody therapies for COVID-19 (i.e., monoclonal antibodies or convalescent plasma), vaccination should be deferred for at least 90 days. This is a precautionary measure until additional information becomes available, to avoid interference of the antibody treatment with vaccine-induced immune responses. This recommendation applies to people who receive passive antibody therapy before receiving any COVID-19 vaccine doses and those who receive passive antibody therapy after the first dose but before the second dose, in which case the second dose should be delayed for at least 90 days after receiving the antibody therapy.

For people receiving antibody therapies not specific to COVID-19 treatment (e.g., intravenous immunoglobulin, RhoGAM), administering mRNA COVID-19 vaccines is unlikely to significantly interfere with the development of a protective antibody response (for vaccine administration either at the same time or any interval before or after receiving antibody therapies). Therefore, there is no recommended minimum interval between other antibody therapies and mRNA COVID-19 vaccination.

CDC

Can I get vaccinated against COVID-19 while I am currently sick with COVID-19?

No. People with COVID-19 who have symptoms should wait to be vaccinated until they have recovered from their illness and have met the criteria for discontinuing isolation; those without symptoms should also wait until they meet the criteria before getting vaccinated. This guidance also applies to people who get COVID-19 before getting their second dose of vaccine.

The COVID-19 vaccine is recommended for all solid organ transplant candidates and recipients provided they do not have a severe allergy to any of the ingredients in the vaccine. Likewise, families and household members of those having a transplant should get vaccinated against the coronavirus as soon as CDC and local guidelines, as well as vaccine quantity, allow.

Because transplantation involves immunosuppression, which can make the vaccine ineffective, those awaiting transplants should, ideally, get a complete COVID-19 vaccination regimen before their transplant. However, the vaccine series should be completed two weeks before the transplant is scheduled. If a patient does not get vaccinated before the procedure, the vaccine should be delayed for one to six months after surgery or for as long as his or her doctor recommends.

What if I received my second vaccination earlier than recommended?

You should not get the second vaccine dose earlier than the recommended times. But, if you've already received your second shot, and it was early by 4 days, or less than the recommended time window, your vaccinations are OK, and you do not need to repeat the vaccination series

CDC

- People are considered fully vaccinated:
- 2 weeks after their second dose in a 2-dose series, like Pfizer or Moderna vaccines, or
- 2 weeks after a single-dose vaccine, like Johnson & Johnson's Janssen vaccine
- If it has been less than 2 weeks since your shot, or if you still need to get your second dose, you are NOT fully protected.

What's Changed

- If you've been fully vaccinated:
- You can gather indoors with fully vaccinated people without wearing a mask.
- You can gather indoors with unvaccinated people from one other household (for example, visiting with relatives who all live together) without masks, unless any of those people or anyone they live with has an increased risk for severe illness from COVID-19.
- COVID-19 exposure: not need to get tested or isolaion , unless having symptoms.: unless living in a group setting

What Hasn’t Changed

- if you’ve been fully vaccinated:
- You should still take steps to protect yourself and others in many situations, like wearing a mask, staying at least 6 feet apart from others, and avoiding crowds and poorly ventilated spaces. Take these precautions whenever you are:
  - In public
  - Gathering with unvaccinated people from more than one other household
  - Visiting with an unvaccinated person who is at increased risk of severe illness or death from COVID-19 or who lives with a person at increased risk
- You should still avoid medium or large-sized gatherings.
- You should still watch out for symptoms of COVID-19, especially if you’ve been around someone who is sick.

World Health Organization

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- The COVAX AMC is the financing instrument that will support the participation of 92 lower-middle and low-income economies in the COVAX Facility
- to ensure equitable access to COVID-19 vaccines, regardless of income level – and requires an urgent investment of US$ 2 billion, from independent donors, philanthropies and the private sector, by the end of 2020.

Thanks for your attention