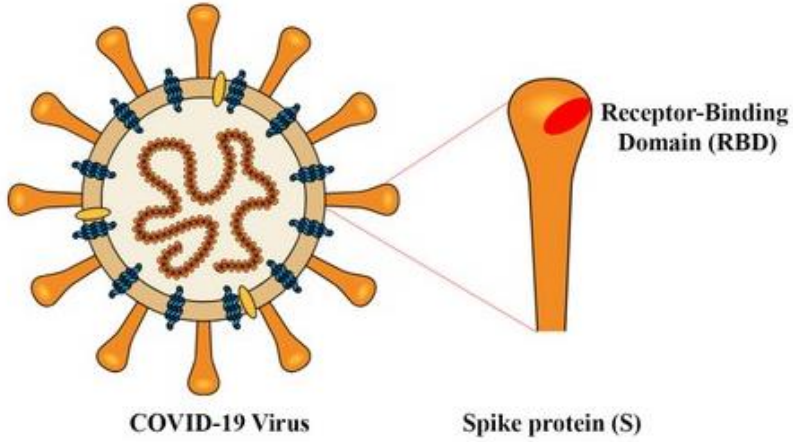
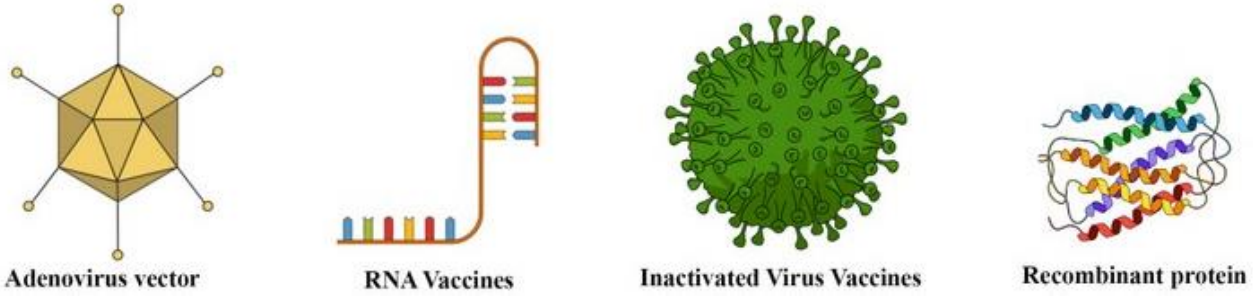
Principles in the Development of inactivated COVID-19 Vaccines



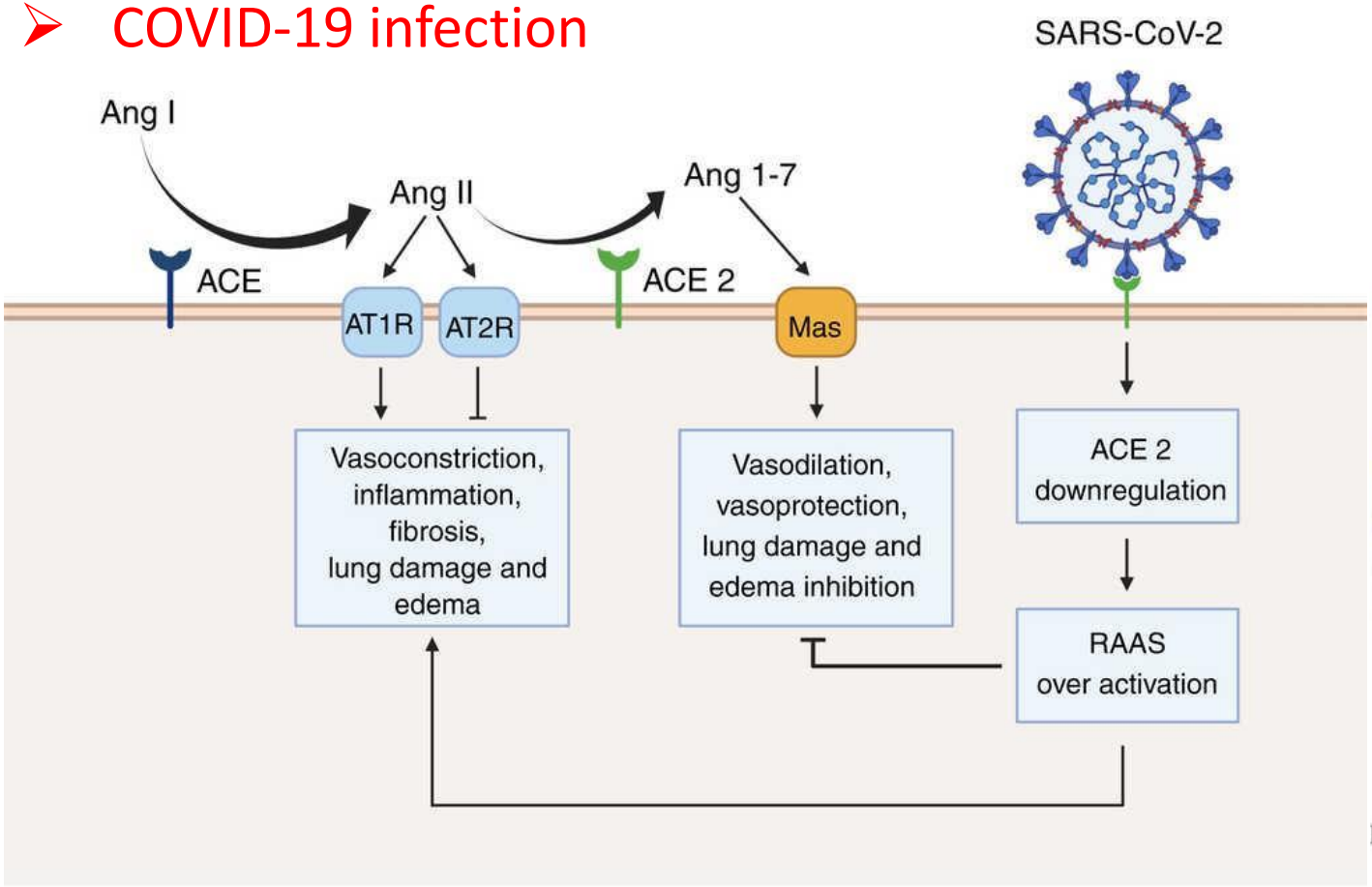


Dr. Molavi, Associate Professor of Pharmaceutical Biotechnology
Tabriz University of Medical Sciences
Winter 1400

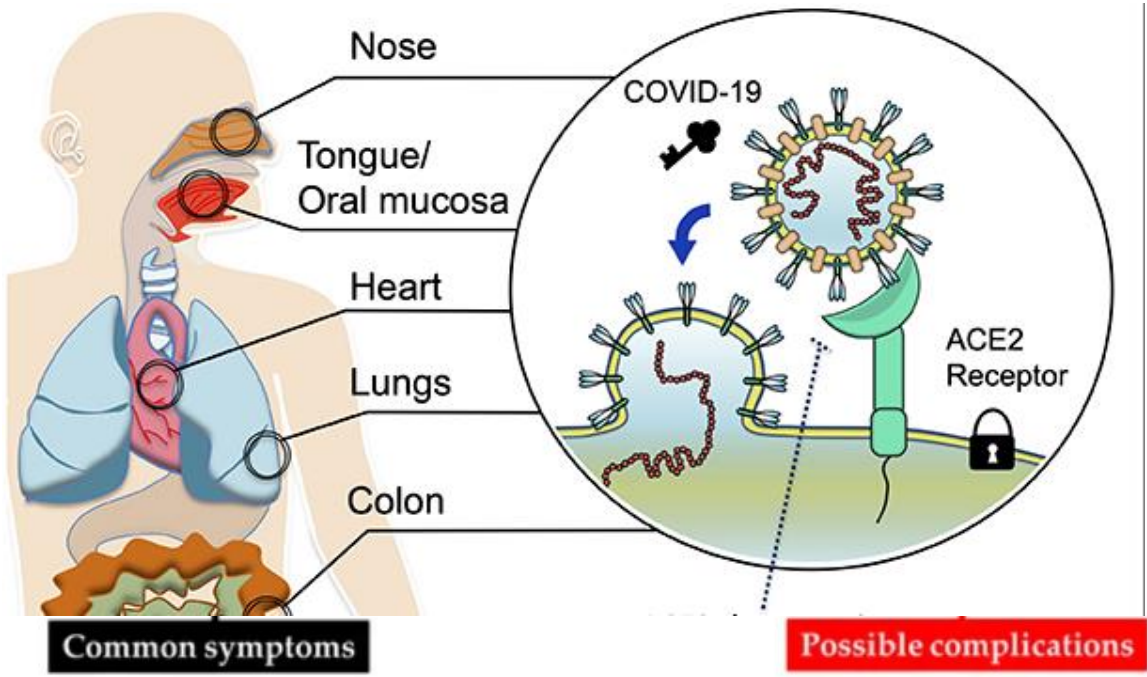
Outline:

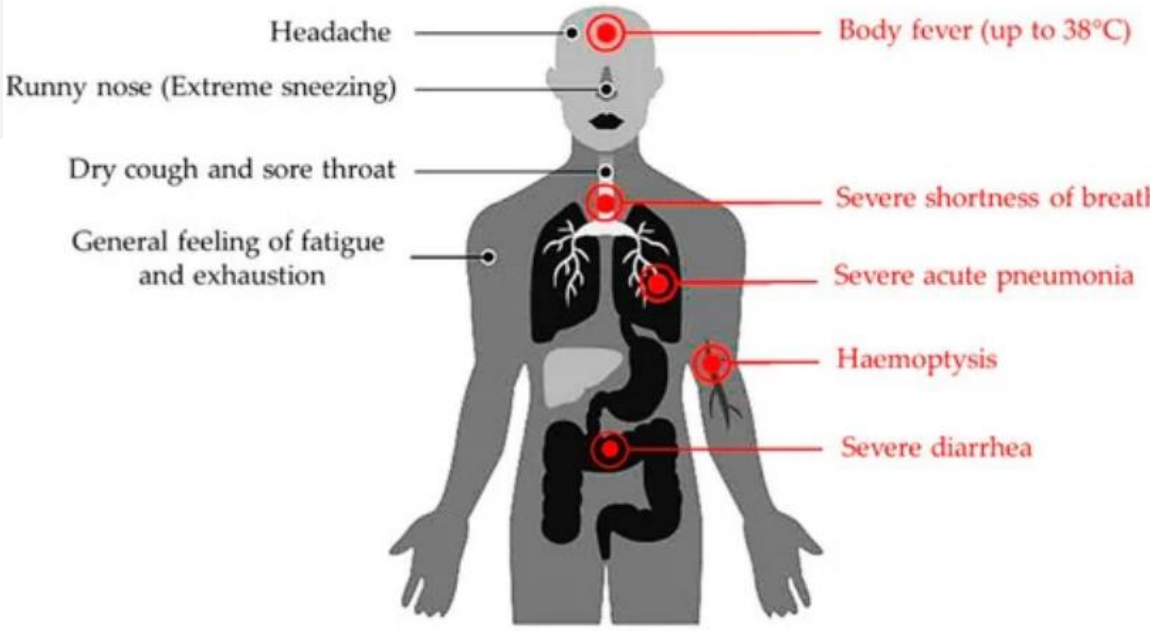
- COVID-19 infection
- Immune response to viral infection
- Vaccine design for COVID-19
- Factors influencing the efficacy of the designed vaccine for protection against corona infection
- Overview of the leading COVID-19 vaccines approved for emergency use
  - Inactivated vaccine
  - Subunit vaccine
  - Viral vector vaccines
  - mRNA vaccines
- Concluding remarks

➢ COVID-19 infection



Rev Col Cardiol. 2020;27:129–31



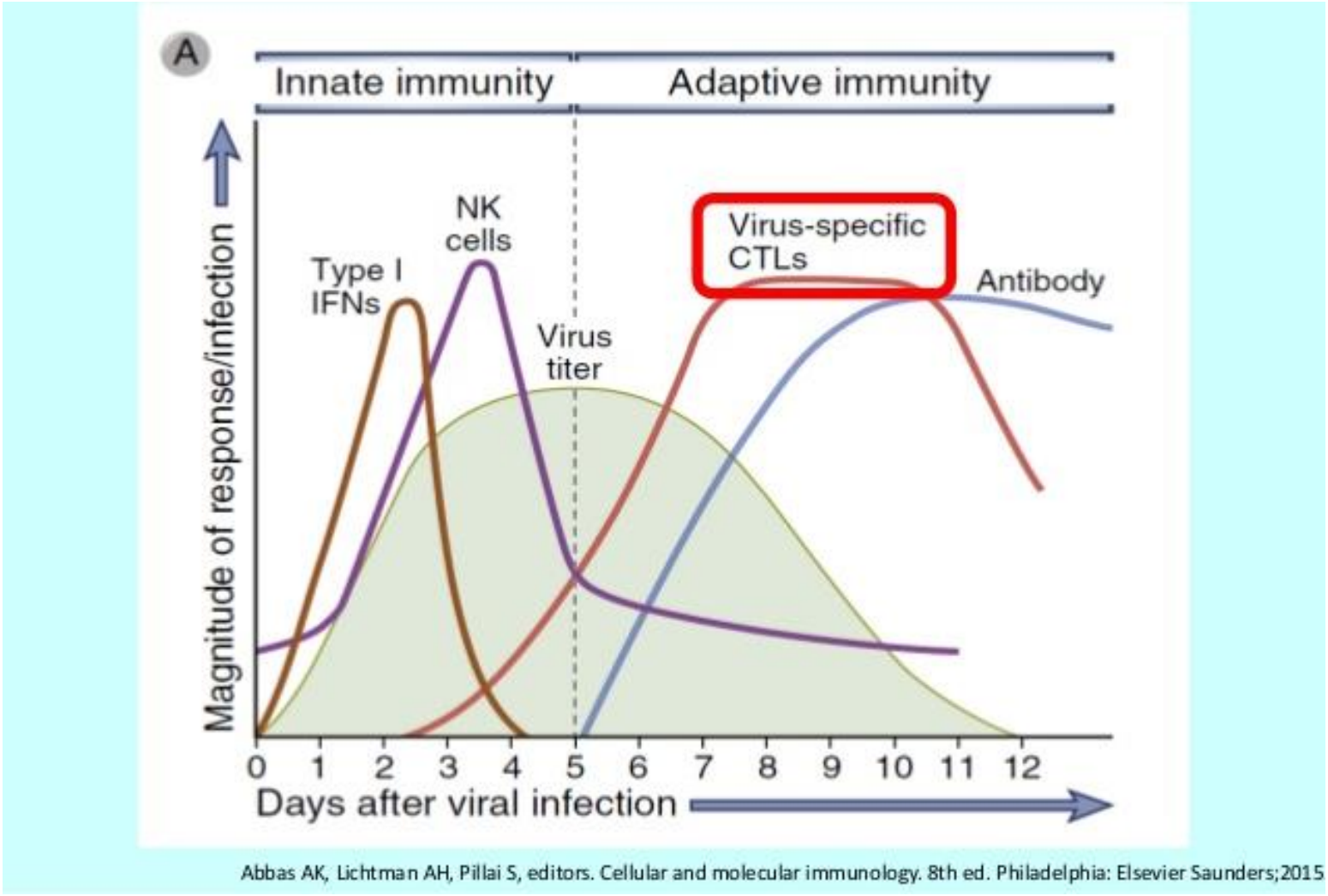


ACE2 receptors are highly expressed in various body organs in particular in the nasal and oral mucosa, the tongue, and in ciliated epithelial cells in the upper and lower airway and in type II pneumocytes in the alveoli in the lower airway.

Immune responses to a viral infection

Innate Immunity: General immediate responses to ANY type of infection

Adaptive/Specific Immunity: Specific response to an infection Involves the **cellular response** (T cells) and the **antibody response** (B cells)

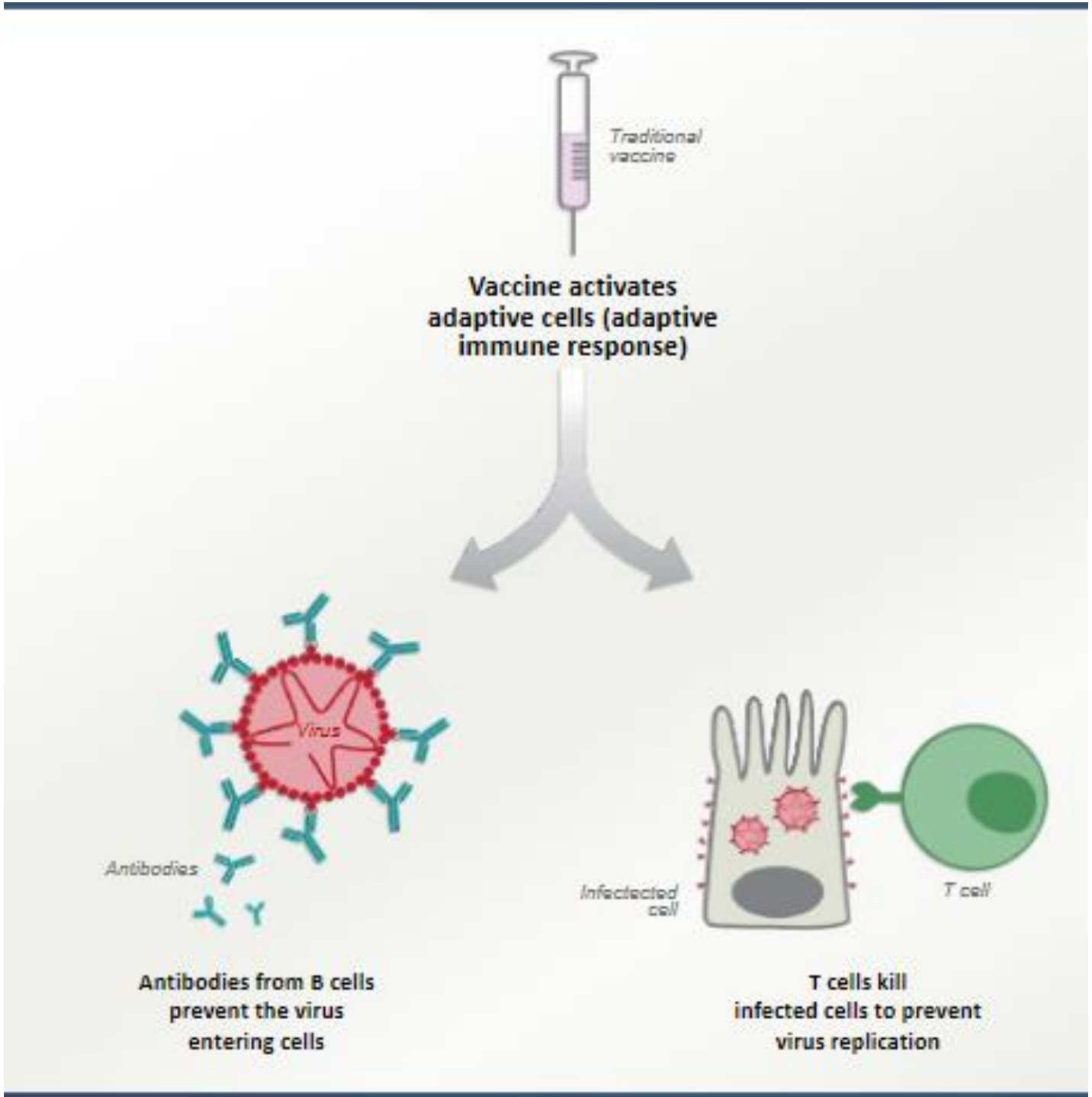


Abbas AK, Lichtman AH, Pillai S, editors. Cellular and molecular immunology. 8th ed. Philadelphia: Elsevier Saunders;2015

Innate immune response is immediate; whereas cellular & antibody response usually starts after 6 to 8 days

Induction of both Involves the **cellular response** (T cells) and the **antibody response** are needed to fight a viral infection and induce immunity to the viral infection

An effective vaccine against a viral infection will induce both humoral and cellular immune response



Principles of vaccine development for an infectious disease

Two main parts of a vaccine

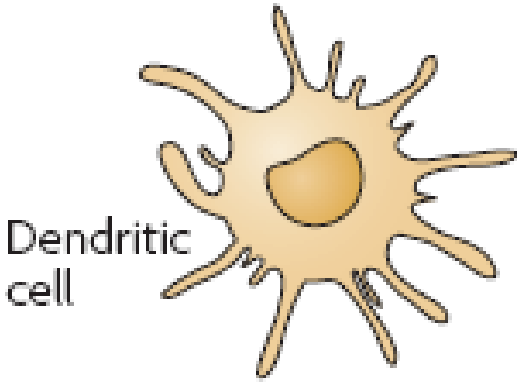
1) Antigen/Immunogen
2) Adjuvant

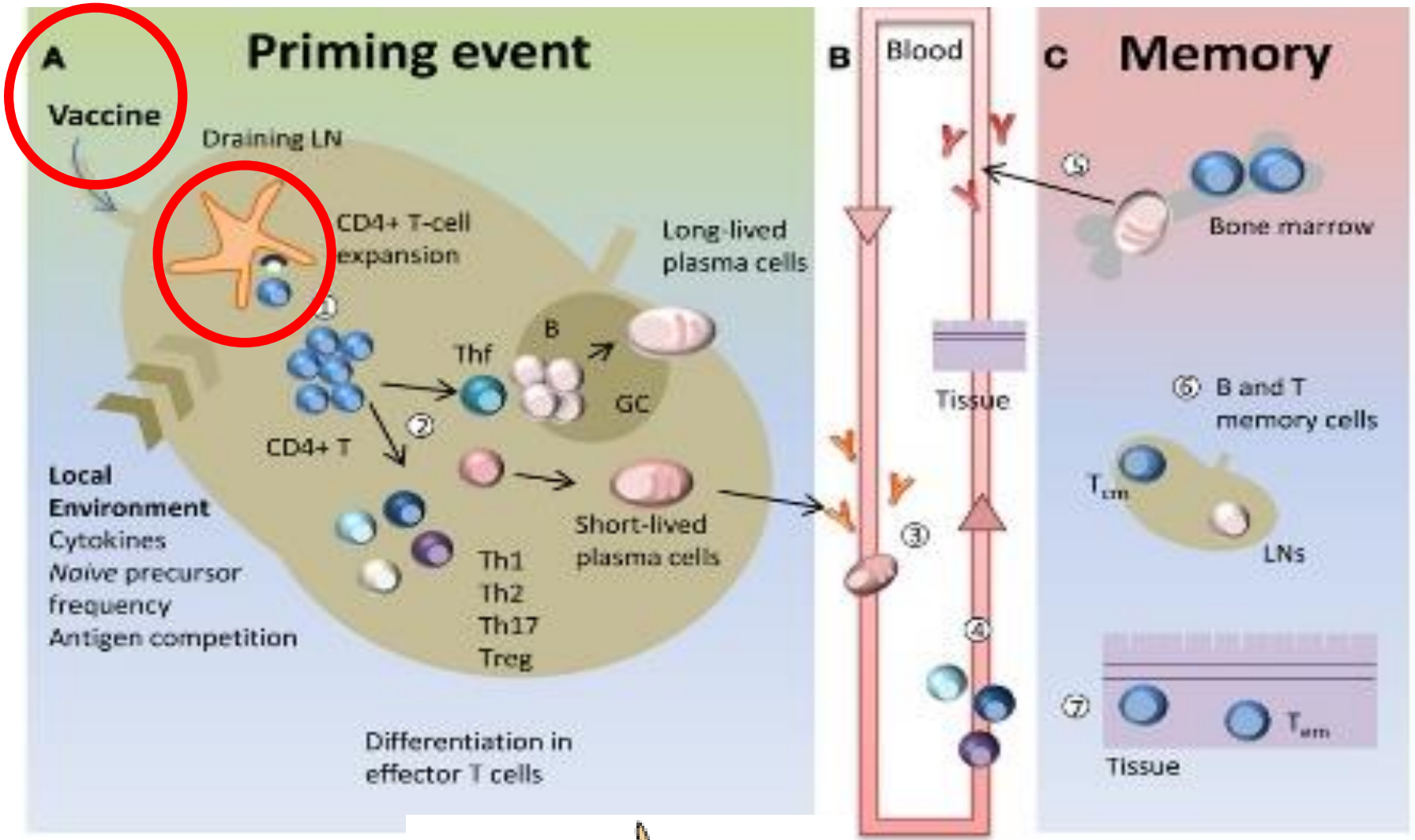
Inactivated virus | Viral subunit | Viral vector | RNA vaccines

Table. Advantages and disadvantages of immunogens used in vaccines

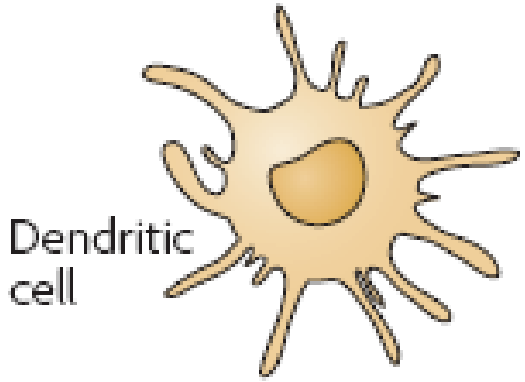
IMMUNOGEN	WHAT IT IS	ADVANTAGE	DISADVANTAGE	EXAMPLE OF VACCINES
Inactivated virus	Inactivated dead virus	Induces strong antibody response	Requires large quantities of virus, low or no cellular response	Influenza, rabies hepatitis A
Viral subunit	A protein derived from a pathogen	May have fewer side effects than whole virus (redness, swelling at injection site)	May be poorly immunogenic; complex process	Influenza
Viral vector	Viral pathogen expressed on a safe virus that doesn't cause disease	Rapid development, strong cellular response, relatively easy to produce	Prior exposure to vector virus (eg. adenovirus) may reduce immunogenicity, some vectors require boosting with a different vector	Ebola
Nucleic acid	mRNA coding for a viral protein	Strong cellular immunity; rapid development	Relatively low antibody response	COVID-19

Target cells for vaccines are **dendritic cells**



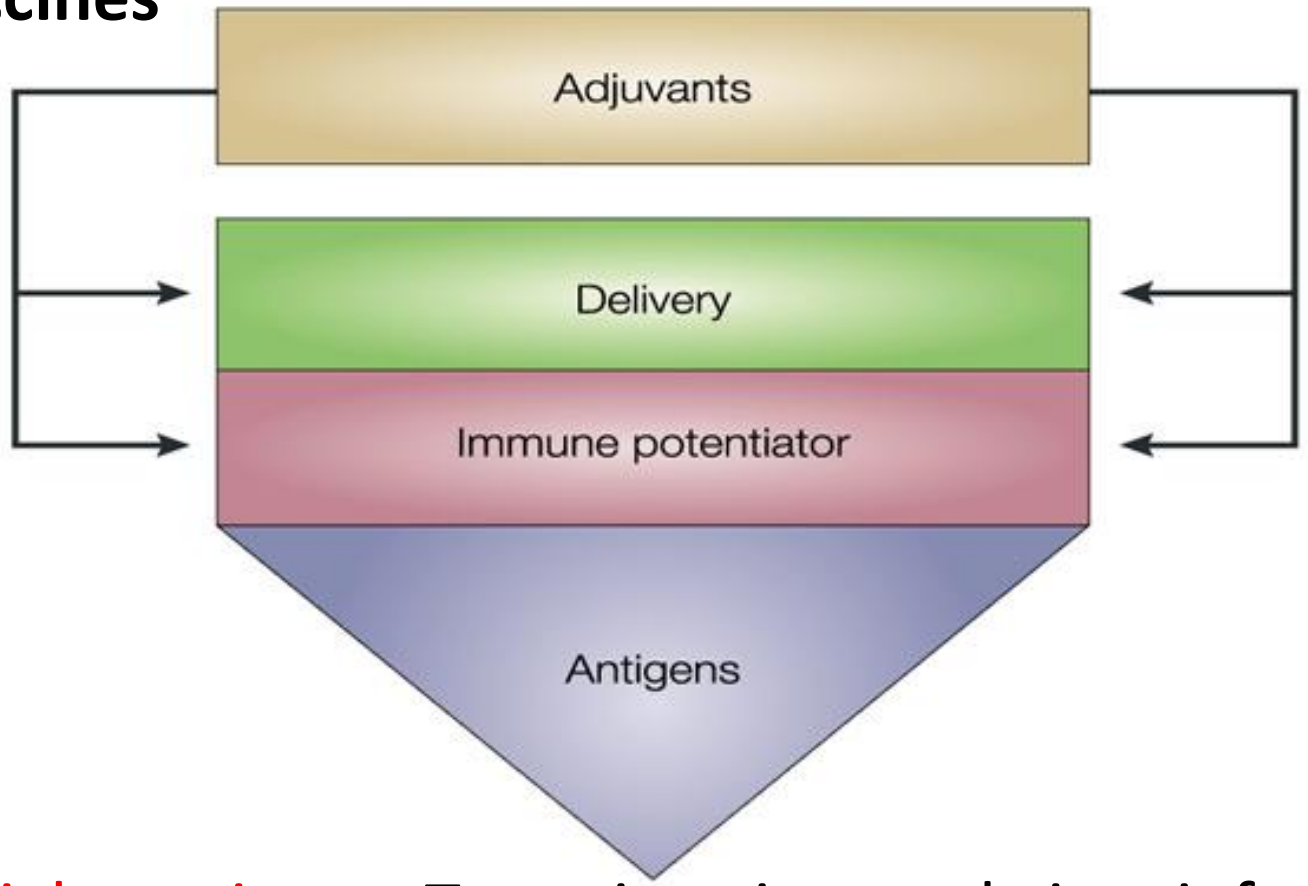


Innate Immunity



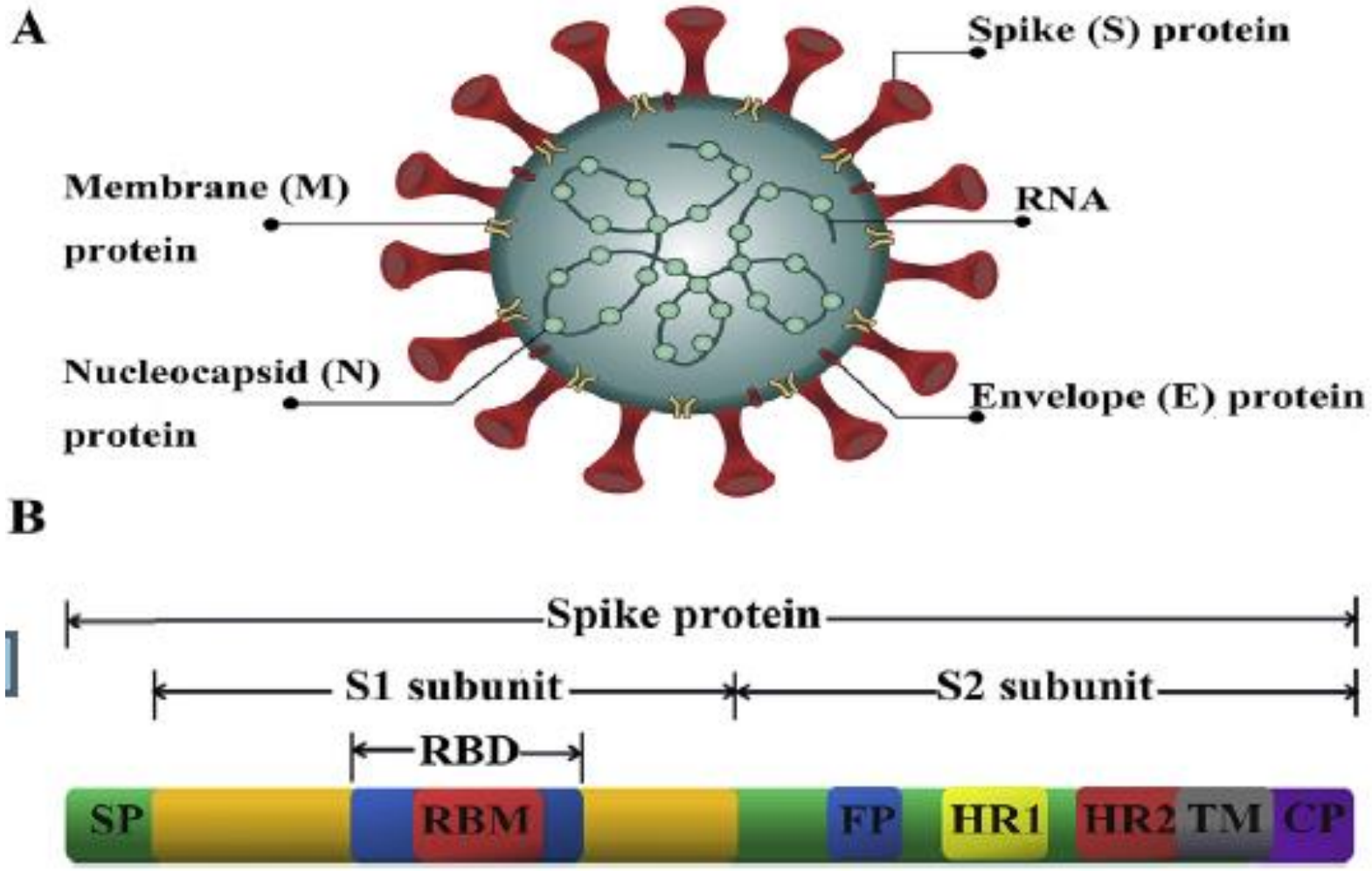
Adaptive Immunity

Factors Influencing the Efficacy of a vaccine developed for a viral infection i.e COVID-19 Vaccines



1) Targeting the right antigens: Targeting virus and virus infected cells to the immune system - neutralizing virus and preventing its entry to the cells
2) Induction of both humoral and cell-mediated immune responses by the selection of the right type of adjuvant and antigen delivery

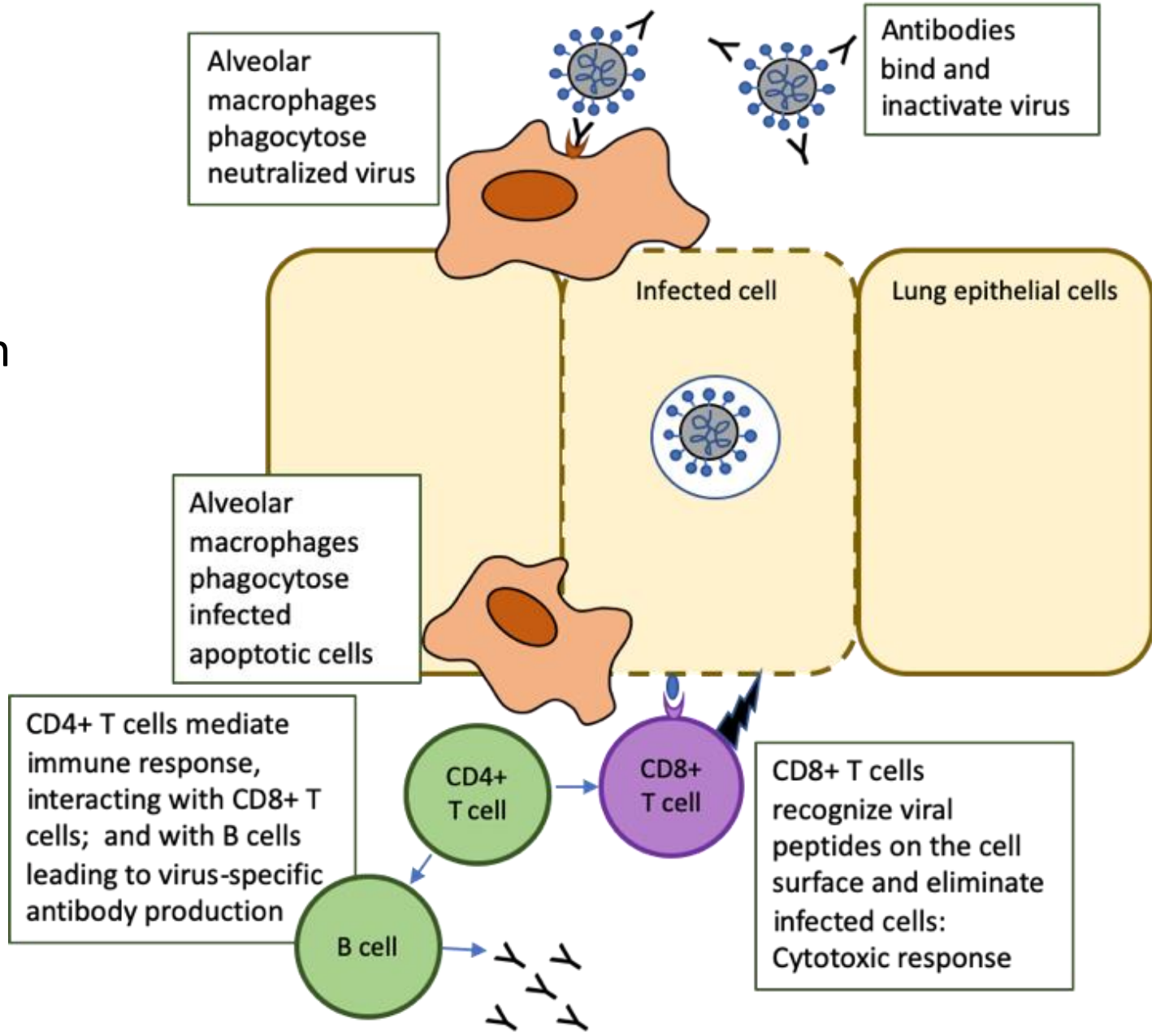
Corona virus structural proteins



Many COVID-19 candidate vaccines were designed to use the SARS-CoV-2 spike protein (S protein) or part of it as the immunogen, an agent capable of inducing immune responses

Humoral responses: Anti-S protein antibodies neutralize the viruses and prevent its binding and entry to the cells through ACE2 receptors. The antibodies also target the virus particles to the cell of immune system for destruction

Cell mediated immune responses:
CTL destroy the virus infected cells



Selection of antigen

Table 1
Select recombinant protein vaccine candidates in clinical trials for COVID-19 as of December 8, 2020 [5]

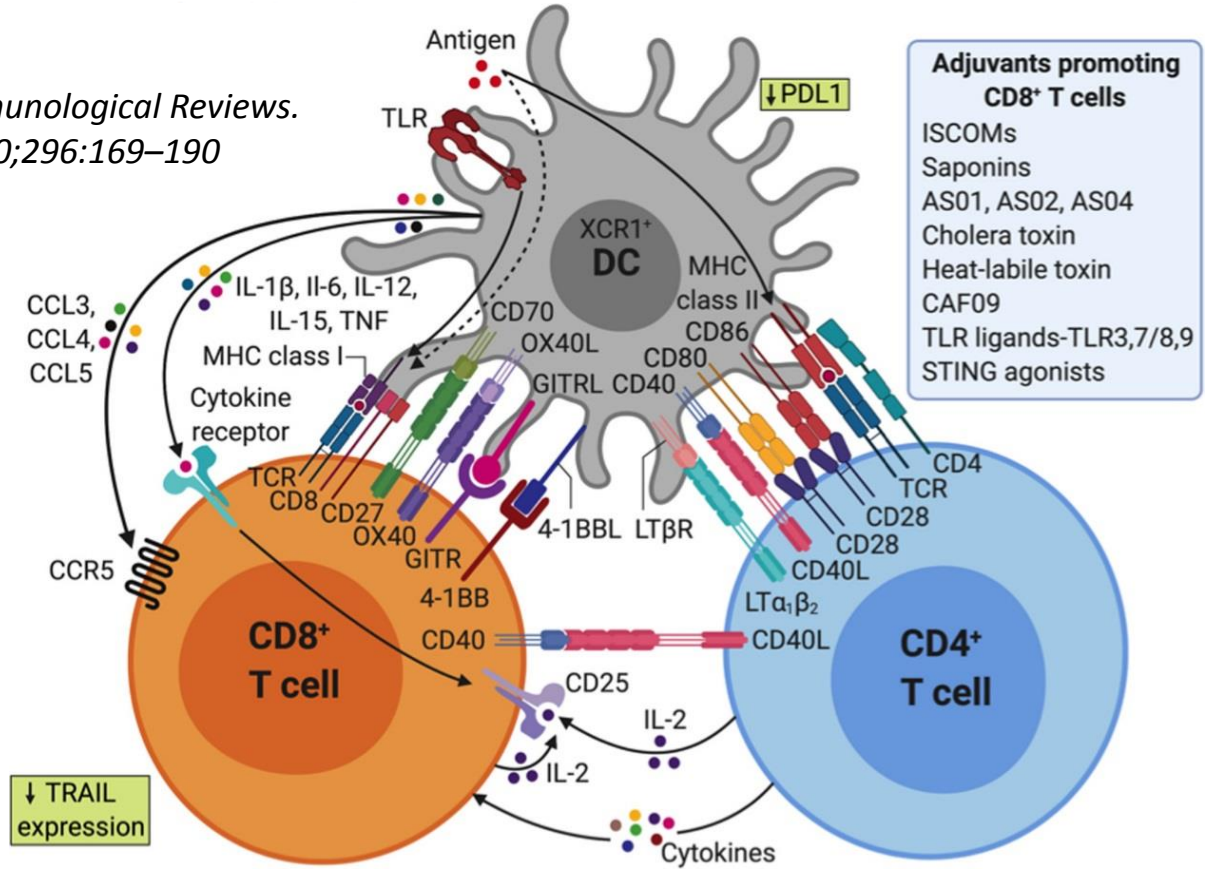
Antigen	Vaccine developer	Platform/technology	Adjuvants	Most advanced clinical stage	References
Full-length S-protein based vaccines					
Trimer	Novavax	Insect cells	Matrix M	Phase 3	[6–8]
S-protein	Sanofi Pasteur/GSK	Insect cells	2 different adjuvants (likely variants of AS03)	Phase 1 (to be repeated)	[9]
SCB-2019 trimer	Clover Biopharmaceuticals Inc./GSK/Dynavax	CHO cells	Alum+CpG 1018 or AS03	Phase 1	[10,11]
S-2P (MVC-COV1901)	Medigen Vaccine Biologics Corporation/NIAID/Dynavax	CHO cells	Alum+CpG1018	Phase 1	[12,13]
Covax-19	Vaxine Pty Ltd/Medytox	Insect cells	AdvaxCpG55.2	Phase 1	[14,15]
RBD-based vaccines					
AdimrSC-2f	Adimmune	Baculovirus/Sf9	Alum	Phase 1	[16]
SARS-CoV-2-RBDN1C1	Biological E/BCM	Yeast	Alum+CpG	Phase 1-2	[17–19]
FINLAY-FR-1/2	Instituto Finlay de Vacunas, Cuba			Phase 1	[20,21]
KBP-201	Kentucky Bioprocessing, Inc	Plants		Phase 1-2	[22]
RBD Dimer	Anhui Zhifei Longcom Biopharmaceutical/Institute of Microbiology, Chinese Academy of Sciences	CHO Cells	Aluminum preparation	Phase 3	[23,24]
RBD	West China Hospital, Sichuan University P	Insect Cells	Alum	Phase 2	[25–27]
Multi-epitope vaccines					
Multitope Peptide-based Vaccine (MPV)	COVAXX	Peptides	CpG and alum (AdjuPhos®)	Phase 1	[28,29]
EpiVacCoron	Vektor Laboratories, Russia	Chemical synthesis	Alum	Phase 1	[30]
CoVac-1	University Hospital Tübingen	Peptides	Montanide ISA51	Phase 1	[31,32]

Selection of adjuvants

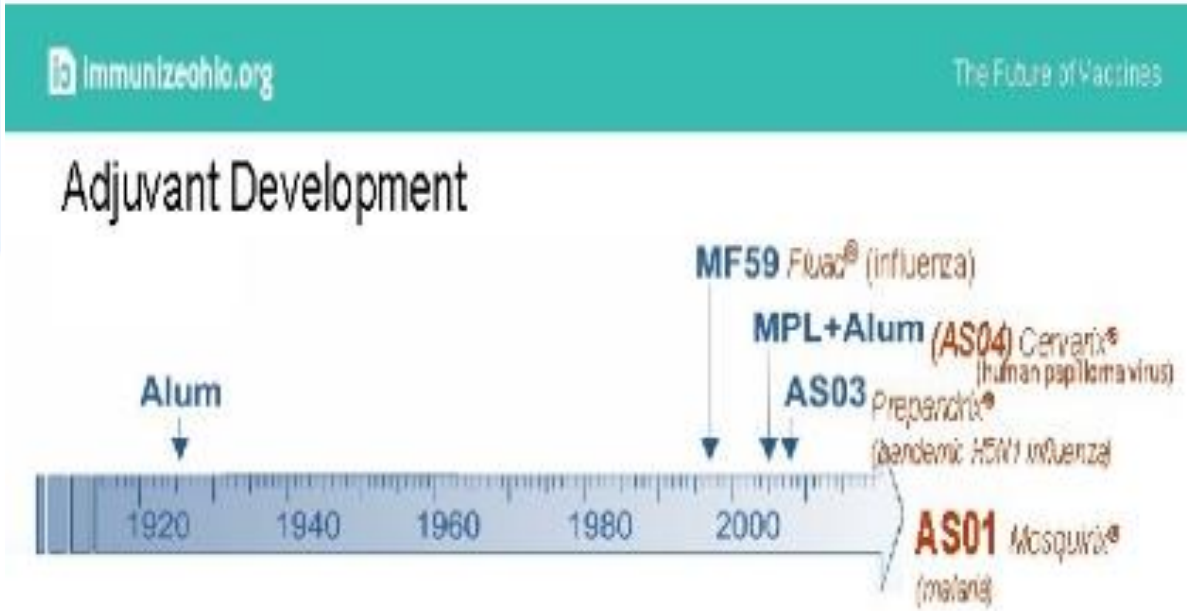
Table 2
List of adjuvants used in recombinant protein COVID-19 vaccine candidates currently tested in the clinic.

Name	Components	Receptor/pathway	Disease target tested in the clinic
Alum[a]	Aluminum salts (aluminum hydroxide, aluminum phosphate)	NLRP3 uric acid, DNA	Anthrax[a], Diphtheria[a], Tetanus[a], Pneumococcus[a], hepatitis A[a] Hepatitis B[a], Japa Meningococcal B[a] and C[a], human papillomavirus[a], SARS, COVID-19
MF59[a], AS03[a]	Oil-in-water emulsion squalene oil plus surfactants	MyD88, ASC, ATP	Influenza[a], COVID-19
CpG 1018[a]	Synthetic DNA alone or formulated with Alum	TLR9	Hepatitis B[a], Malaria, Influenza, Anthrax, Cancer, COVID-19
Matrix M/IscoMatrix	Saponin	Unknown	Hepatitis C, Influenza, HSV, human papillomavirus, Malaria, Cancer, COVID-19
Advax	polysaccharide particle made	Unknown	HIV, Influenza, Hepatitis B, COVID-19

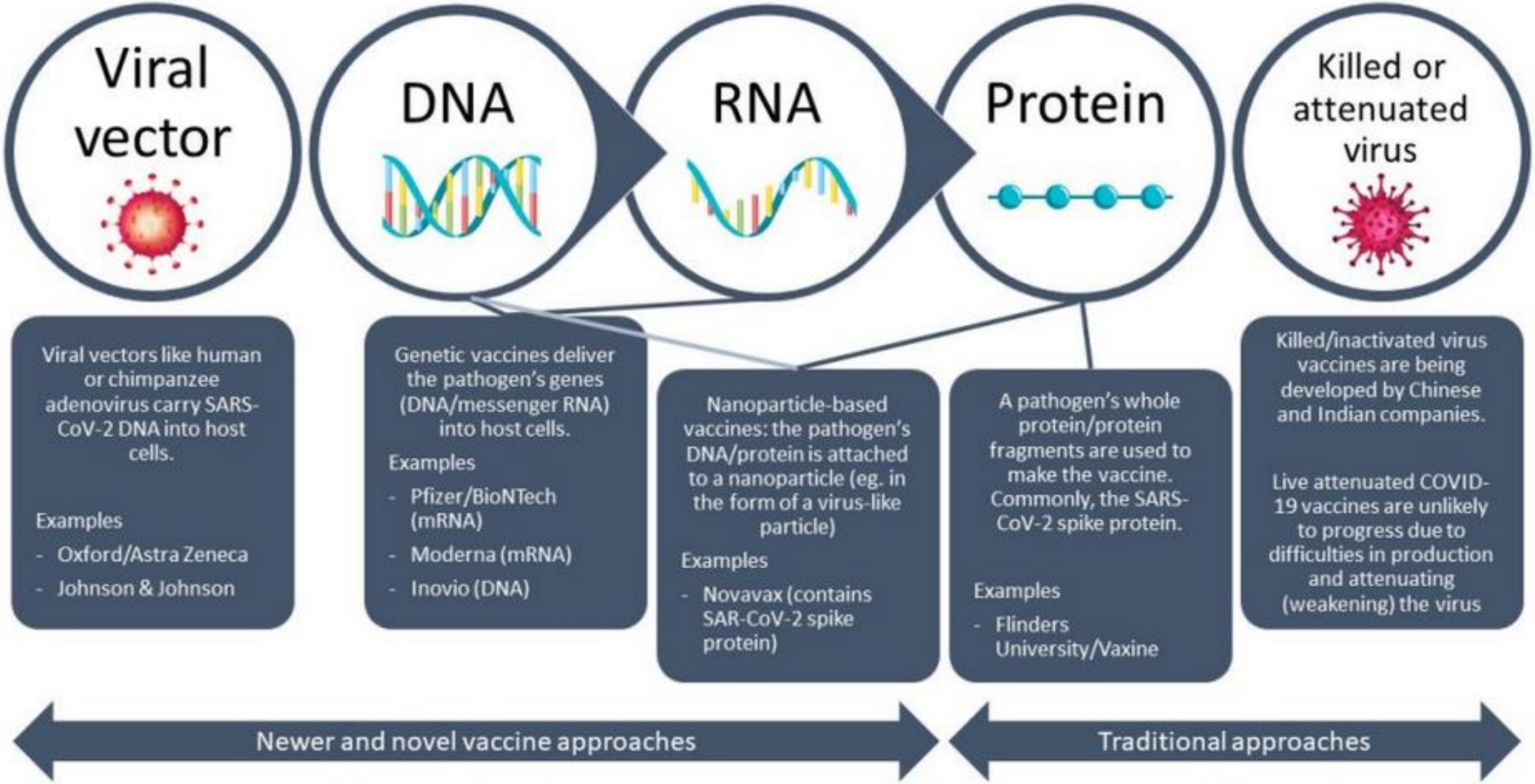
Immunological Reviews. 2020;296:169–190



Adjuvants promoting CD8⁺ T cells
ISCOMs
Saponins
AS01, AS02, AS04
Cholera toxin
Heat-labile toxin
CAF09
TLR ligands-TLR3,7/8,9
STING agonists



Multiple vaccine platforms have been explored for COVID-19 vaccine development as each vaccine platform has unique advantages and disadvantages



By the end of February 2021, a total of 256 COVID-19 vaccine candidates have been developed, with 108 in clinical trials and ~150 in preclinical studies.

Platform		Candidate vaccines (no. and %)	
PS	Protein subunit	36	33%
VVnr	Viral Vector (non-replicating)	16	15%
DNA	DNA	10	9%
IV	Inactivated Virus	16	15%
RNA	RNA	18	17%
VVr	Viral Vector (replicating)	2	2%
VLP	Virus Like Particle	5	5%
VVr + APC	VVr + Antigen Presenting Cell	2	2%
LAV	Live Attenuated Virus	2	2%
VVnr + APC	VVnr + Antigen Presenting Cell	1	1%
		108	

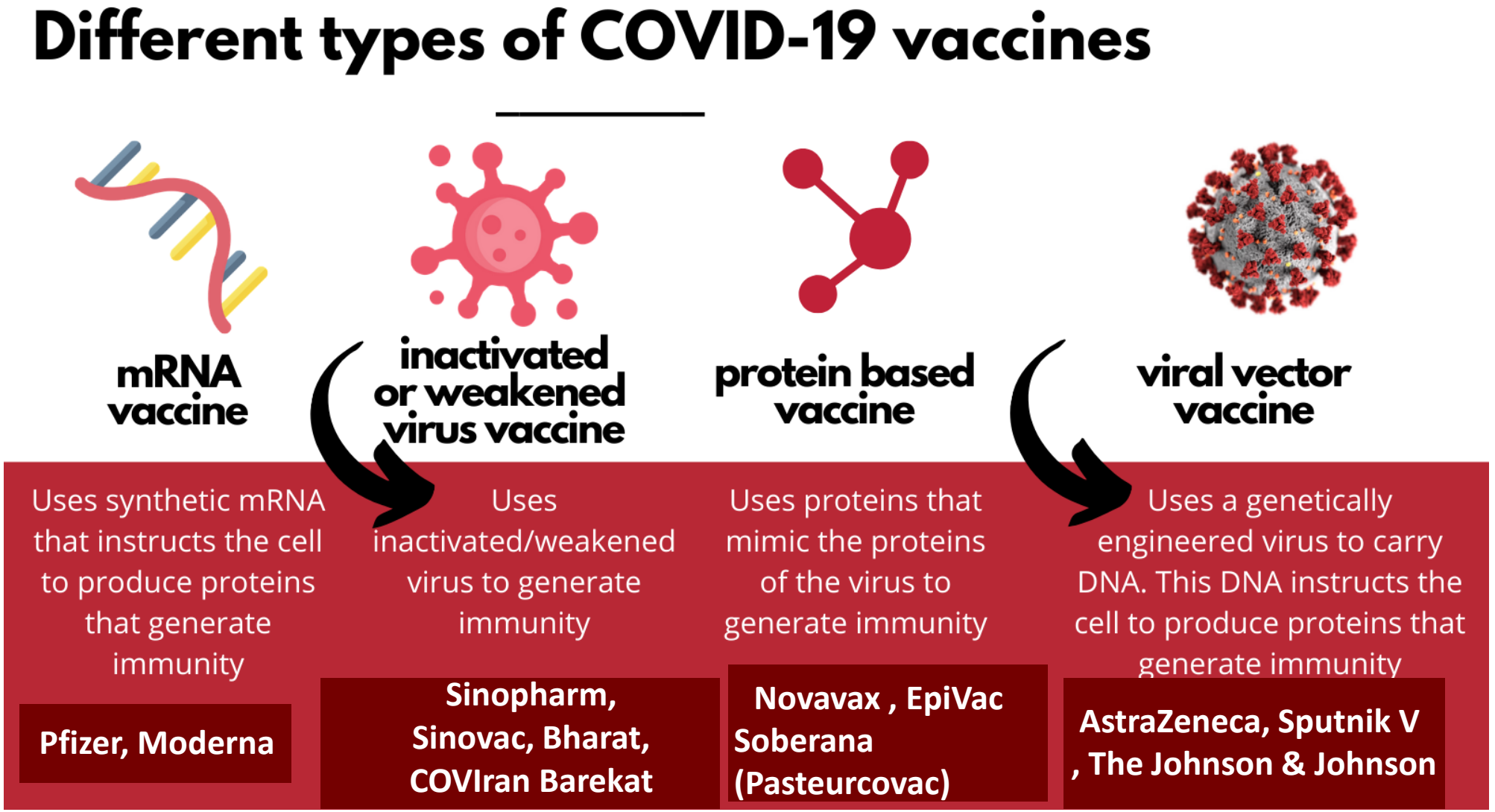
A Comprehensive Review of the Global Efforts on COVID-19 Vaccine Development,
Yingzhu Li et al, ACS Cent. Sci. 2021, 7, 512–533

WHO, Coronavirus Vaccine Tracker

Leading vaccines

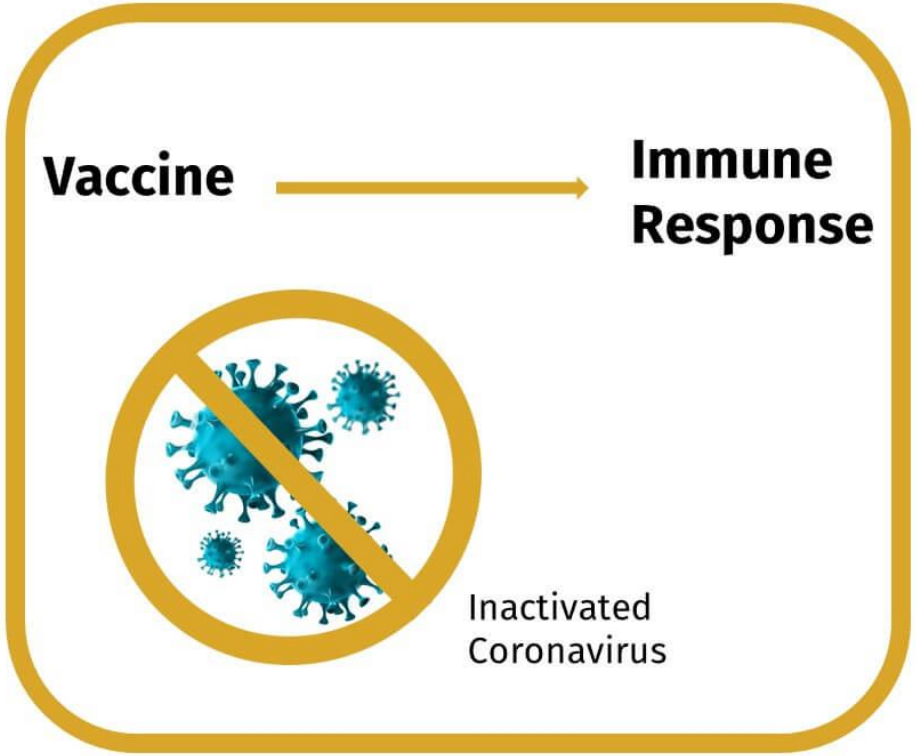
Developer	How It Works
Pfizer-BioNTech	mRNA
Moderna	mRNA
Gamaleya	Ad26, Ad5
Oxford-AstraZeneca	ChAdOx1
CanSino	Ad5
Johnson & Johnson	Ad26
Vector Institute	Protein
Novavax	Protein
Sinopharm	Inactivated
Sinovac	Inactivated
Sinopharm-Wuhan	Inactivated
Bharat Biotech	Inactivated

Leading COVID-19 vaccines which will be briefly discussed in this webinar



1) Inactivated vaccines

The oldest and most well-established types of vaccine (hepatitis A, polio, and measles vaccines)



Inactivated Virus Vaccine

SARS-CoV2 is chemically inactivated by **beta-propiolactone**. So it cannot replicate but the proteins remain intact.

An inactivated vaccine includes an adjuvant plus the whole inactivated virus. This type of vaccine mainly induce antibody responses. The use of some new generation adjuvants (TLR7/8 ligand) in this type of vaccines leads to the induction both cellular and antibody immune responses and make them more effective for protection against the viral infection

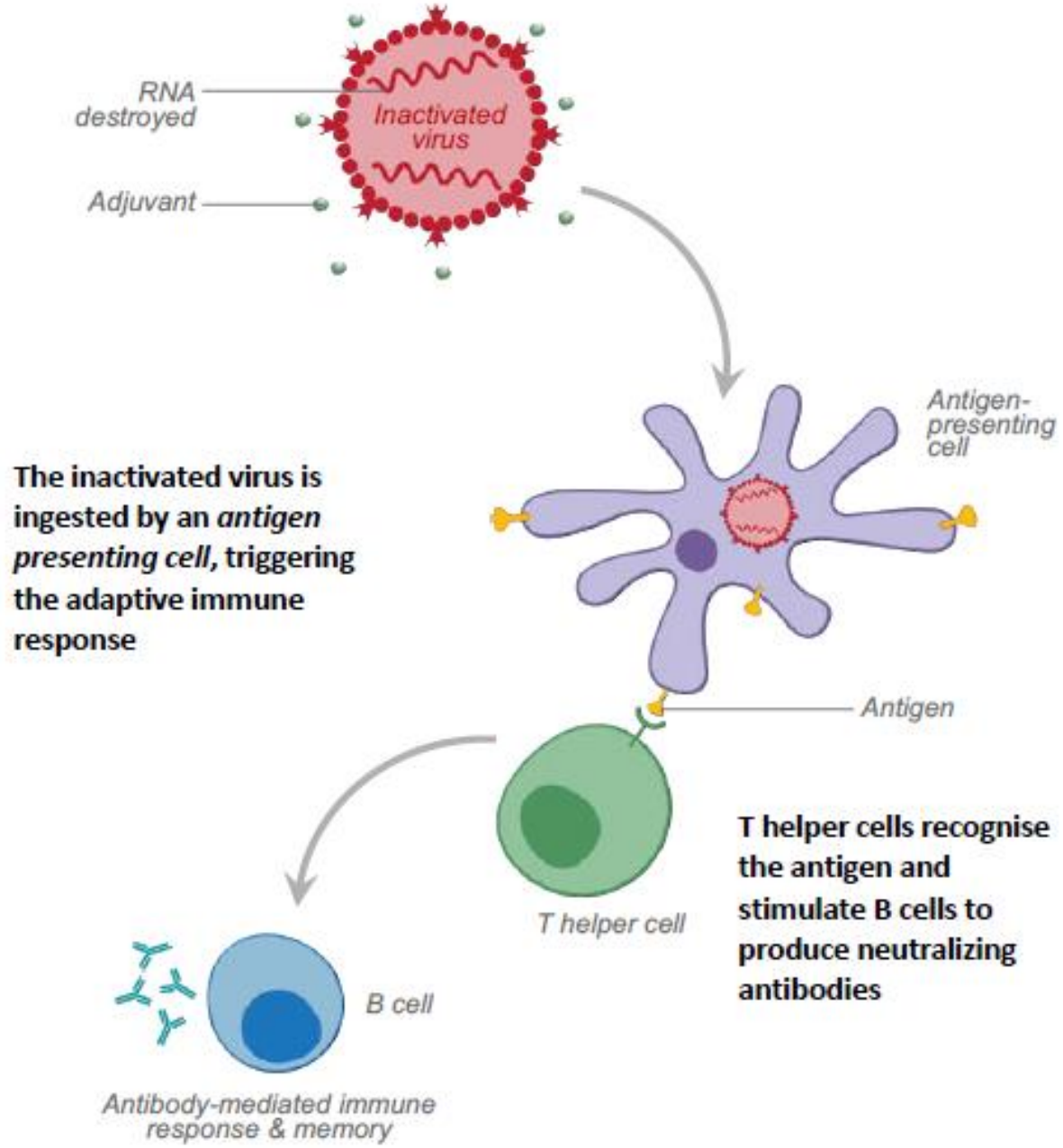
Inactivated vaccines

- In inactivated virus vaccines, **the genetic material of the virus has been destroyed to stop disease producing capacity**

- Inactivated virus cannot replicate inside the body, so higher doses are needed

- an **adjuvant** (molecules that stimulate the immune system) is used to help strengthen the immune response

- Inactivated virus vaccines generally only induce **<u>antibody-mediated immunity</u>** (not cell-mediated immunity)



Inactivated corona vaccines authorized for emergency use

1) **Covaxin (BBV152)** developed by India's Bharat Biotech
2**) Sinopharm** developed by Beijing Institute of Biological Products
3) **Sinopharm** developed by Wuhan Institute of Biological Products
4) **Sinovac** (CoronaVac or PiCoVacc) developed by Sinovac Biotech
5) **COVIran Barekat** developed by Iran' Shafa Pharmed Pars

Efficacy ~ 80 %

The comprehensive and updated information on these vaccines can be found at the following link
https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html

Inactivated vaccines authorized for emergency use

Name	Antigen	Adjuvant	Immune responses
Covaxin (BBV152)	inactivated viruses	Aluminium hydroxide +Imidazoquinoline (TLR7/8 agonists)	Neutralizing antibodies and Virus specific CD4 and CD8 responses
Sinopharm *	inactivated viruses	Aluminium hydroxide	Neutralizing antibodies
Sinovac *	inactivated viruses	Aluminium hydroxide	Neutralizing antibodies
COVIran	inactivated viruses	Aluminium hydroxide	Neutralizing antibodies

* authorized for people ages 59 and younger.

Bharat (Covaxin)

Ella, R. et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: a double-blind, randomised, phase 1 trial. Lancet Infect. Dis. 21, 637–646 (2021)

Ella, R. et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: interim results from a double-blind, randomised, multicentre, phase 2 trial, and 3-month follow-up of a double-blind, randomised phase 1 trial. Lancet Infect. Dis. 21, 950–961 (2021).

Bharat Biotech. *Bharat Biotech and ICMR Announce Interim Results from Phase 3 trials of COVAXIN®; Demonstrates overall Interim Clinical Efficacy of 78% and 100% efficacy against Severe COVID-19 disease, Indian council of medical research April 2021*

Table 1 (cont.) | **Human studies of COVID-19 vaccines with reported efficacy**

Vaccine (developer) (dosing regimen)	Formulation	Efficacy against symptomatic infection (phase III trials)	Effectiveness (post implementation)	Antibody responses in humans	T cell responses in humans
Whole-cell inactivated virus					
CoronaVac (Sinovac Biotech) (3 µg protein, 2 doses, 14–28 days apart)[138,139]	SARS-CoV-2 grown in Vero cells, inactivated with β-propiolactone and adsorbed onto aluminium hydroxide[138]	50–84% after 2 doses[140,141]	–	By day 28 day after second dose, RBD-specific binding antibody detected in 88–97% of participants with a 14-day dosing interval and 99–100% with a 28-day interval; NAb present in 94–100% of individuals 28 days after second dose[138,139]	–
BBIBP-CorV (Sinopharm) (4 µg protein, 2 doses, 21 days apart)[142]	SARS-CoV-2 grown in Vero cells, inactivated with β-propiolactone and adsorbed onto aluminium hydroxide[142]	86% after 2 doses[143]	–	By day 14 after second dose, 46–87% of individuals had binding antibodies; this increased to 92–100% by day 28; all recipients had NAbs by 21 days after second dose[142]	–
WIBP-CorV (Sinopharm) (5 µg protein, 2 doses, 21 days apart)[144]	SARS-CoV-2 grown in Vero cells, inactivated with β-propiolactone and adsorbed onto aluminium hydroxide[144]	73% after 2 doses[145]	–	By day 14 after second dose, 100% of participants had binding antibodies against whole inactivated SARS-CoV-2 and 98% had neutralizing antibodies[144]	–
BBV152 (Bharat Biotech) (6 µg protein, 2 doses, 28 days apart)[146]	SARS-CoV-2 grown in Vero cells, inactivated with β-propiolactone and adsorbed onto aluminium hydroxide and an imidazoquinoline molecule (TLR7/	78% after 2 doses[147]	–	After first dose, 65% of participants had anti-S binding antibodies, increasing to 98% by day 14 after second dose; 48% had NAbs after first dose, increasing to 97% by day 14 after second dose; GMTs for binding and NAbs markedly increased by second dose[100,146]	Strong bias towards a T_H1 cell phenotype (IFNγ and TNF), with minimal T_H2 cell responses (as measured by IL-5 and IL-13) after in vitro stimulation. Increase in $CD4^+CD45RO^+$ memory T cells by day 76 after second dose[100,146]

Nature reviews Immunology August 2021

Efficacy against new variants:

Baharat BBV152 showed a 65.2% protection against the Delta variant in a double-blind, randomized, multicentre, phase 3 clinical trial.

Bernal JL, Andrews N, Gower C, et al. *Effectiveness* of *COVID*-19 *vaccines* against the. B. 1.617. 2 *variant*. medRxiv. 2021 , bioRxiv preprint

JTM Journal of Travel Medicine
International Society of Travel Medicine
Promoting healthy travel worldwide
Established 1991
Journal of Travel Medicine, 2021, 1–3
https://doi.org/10.1093/jtm/taab104
Rapid Communication

Rapid Communication

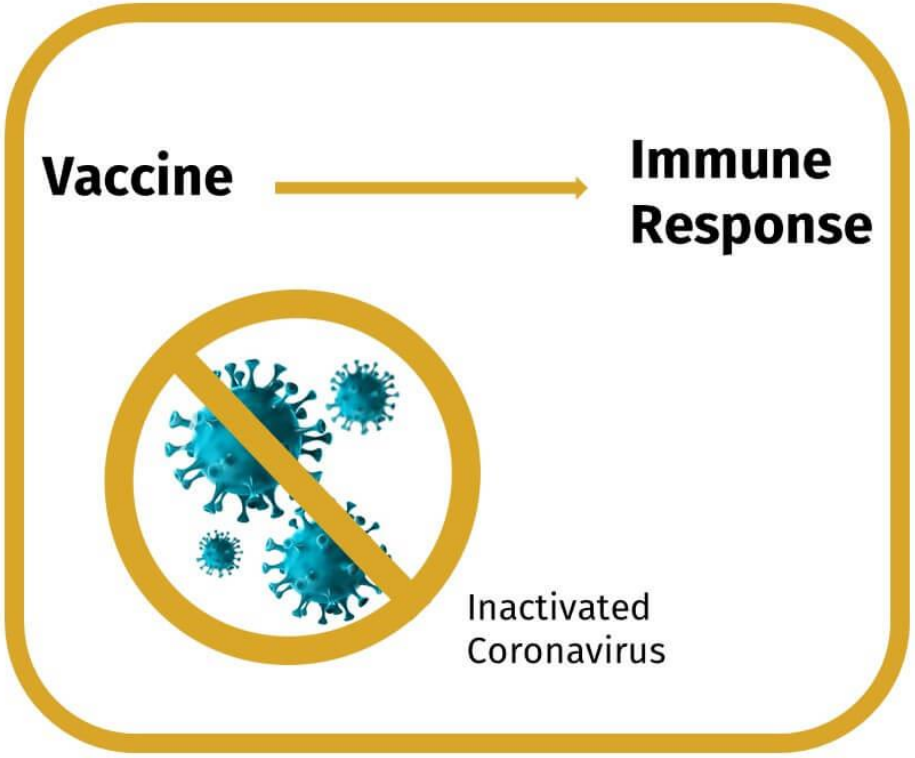
Neutralization of Beta and Delta variant with sera of COVID-19 recovered cases and vaccinees of inactivated COVID-19 vaccine BBV152/Covaxin

Pragya D. Yadav, PhD[1,†,*], Gajanan N. Sapkal, PhD[1,†], Raches Ella, MS[2], Rima R. Sahay, PhD[1], Dimpal A. Nyayanit, PhD[1], Deepak Y. Patil, PhD[1], Gururaj Deshpande, PhD[1], Anita M. Shete, PhD[1], Nivedita Gupta, MD, PhD[3], V. Krishna Mohan, PhD[2], Priya Abraham, MD, PhD[1], Samiran Panda, MD, PhD[3], and Balram Bhargava, DM[3]

[1]Indian Council of Medical Research-National Institute of Virology, Pune, India, [2]Bharat Biotech International Limited,

Inactivated vaccines

	Advantages	disadvantage	vaccine examples
Inactivated	• Broad antigenic profile	• Reduced immune response • Requirement for biosafety facilities • Lower purity	• Hepatitis A • Polio (IPV) • Rabies • Influenza



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