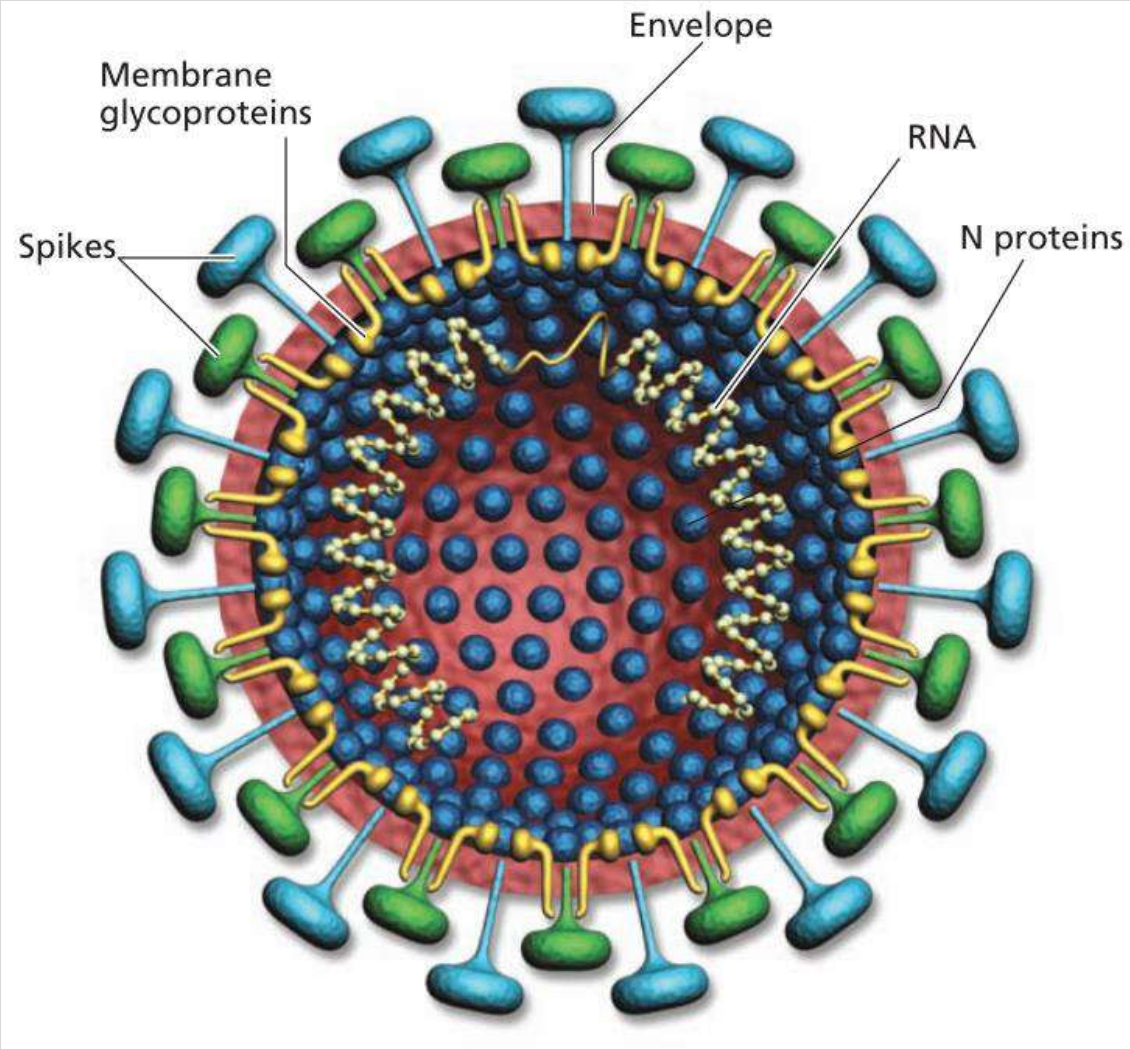
VIROLOGI SARS-COV 2 & KANDIDAT VAKSIN COVID 19

dr. Inayati M.Kes. Sp.M.K.
Laboratorium Mikrobiologi RSUD Kota Yogyakarta

2019-novel Corona Virus (2019-nCoV) ??



Ordo:

- Nidovirales

Familia:

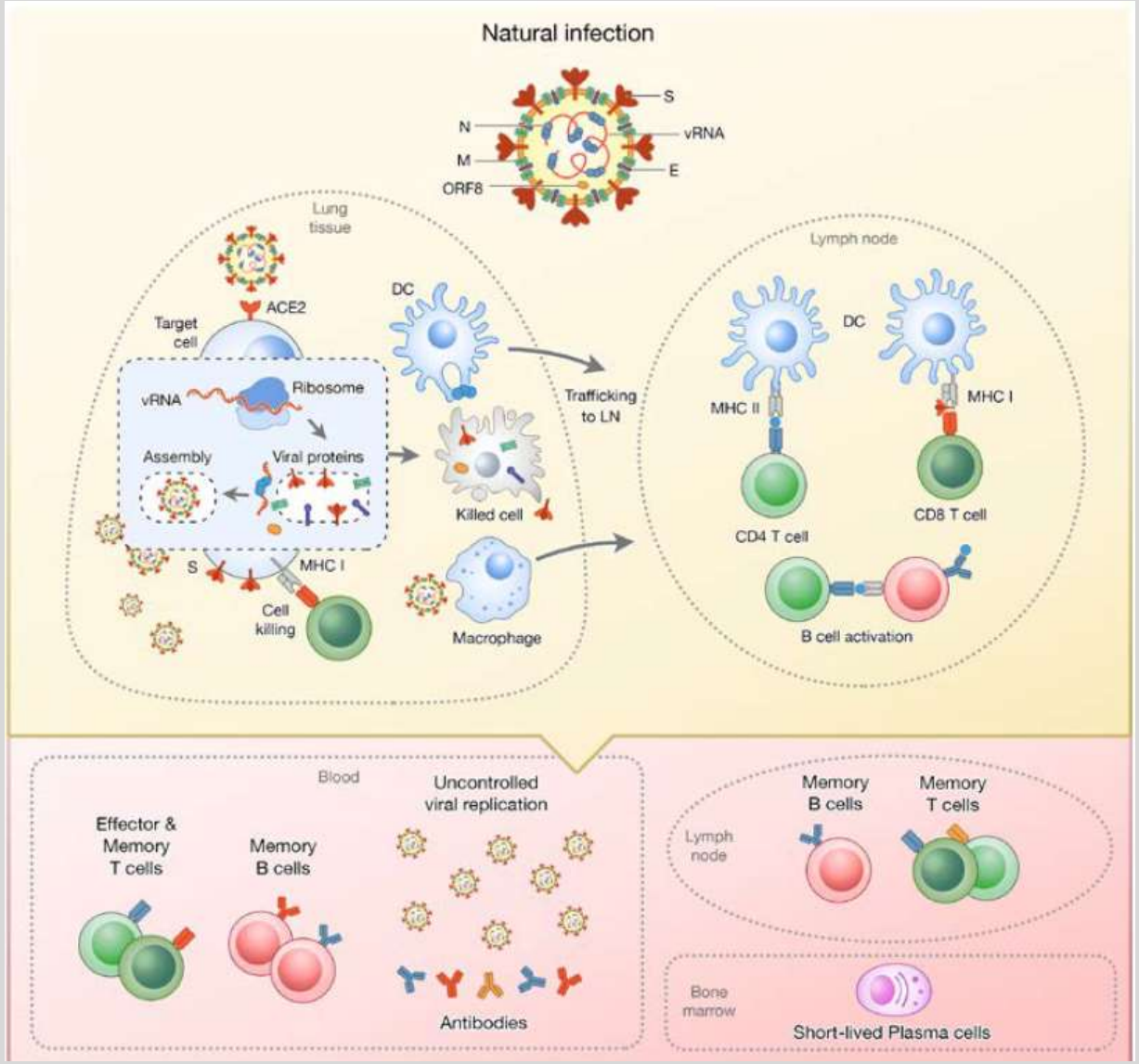
- Coronaviridae

Subfamilia:

- Coronavirinae

Genus:

- Alphacoronavirus
- **Betacoronavirus**
- Gammacoronavirus
- Deltacoronavirus



Youdiil Ophinni, et all, 2020

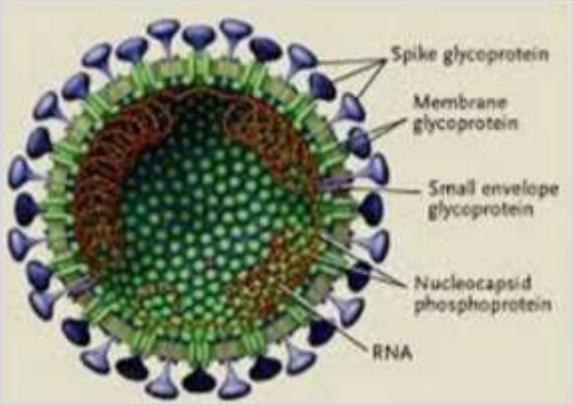
Figure 1. Immunogenesis in the natural infection of SARS-CoV-2

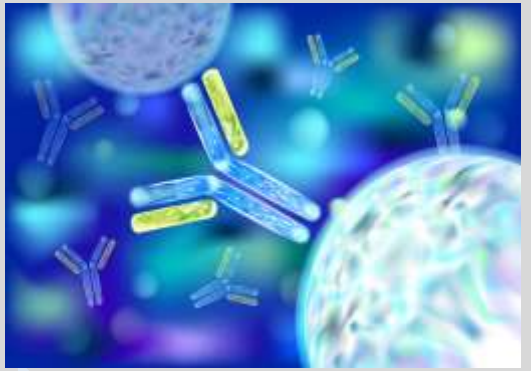
Figure 1. Immunogenesis in the natural infection of SARS-CoV-2

- SARS-CoV-2 infects target cells in the lung tissue via ACE- 2 receptor and coreceptors (not shown), where the virus hijacks host ribosomal process to transcribed its viral RNA (γRNA) into viral proteins, shown as **spike (S, red), matrix (M, green), envelope (E, purple), nucleoprotein (N, blue)** and one of **the six non-structural proteins (ORF8, orange)**.
- Expression of viral proteins from infected cells leads to cell killing by **cytotoxic T or natural killer cells**. Antigen presenting cells (APC) such as dendritic cells (DC) and macrophages **engulf** either viral proteins from killed cells or the whole virion, before trafficking to the lymph node (LN).
- **In the LN**, viral antigens are presented by APC via the major histocompatibility complex (MHC) molecule class I and II to the T cell receptors of naive CD8 and CD4 T cells, respectively, to **initiate activation and differentiation into effector or memory T cells.**
- Naive B cells presenting viral antigens via MHC II are activated by CD4 T cells in the LN, initiating **differentiation into memory B cells and antibody-producing plasma cells.**
- Immune induction from a single infection also results in **short-lived plasma cells** in the bone marrow.
- Produced antibodies are multivalent and may be neutralizing, which is the anti-S antibody, or non-neutralizing to the virus.
- Disease outcome is determined by the arms race between **viral replication** against **humoral and cellular immunity induction.**


CORONAVIRUS
COVID-19
Vaccine
INJECTION ONLY

VAKSIN





Suspensi Bagian-bagian Produk Mikroorganisme

Dilemahkan atau Dimatikan

menginduksi sistem imun

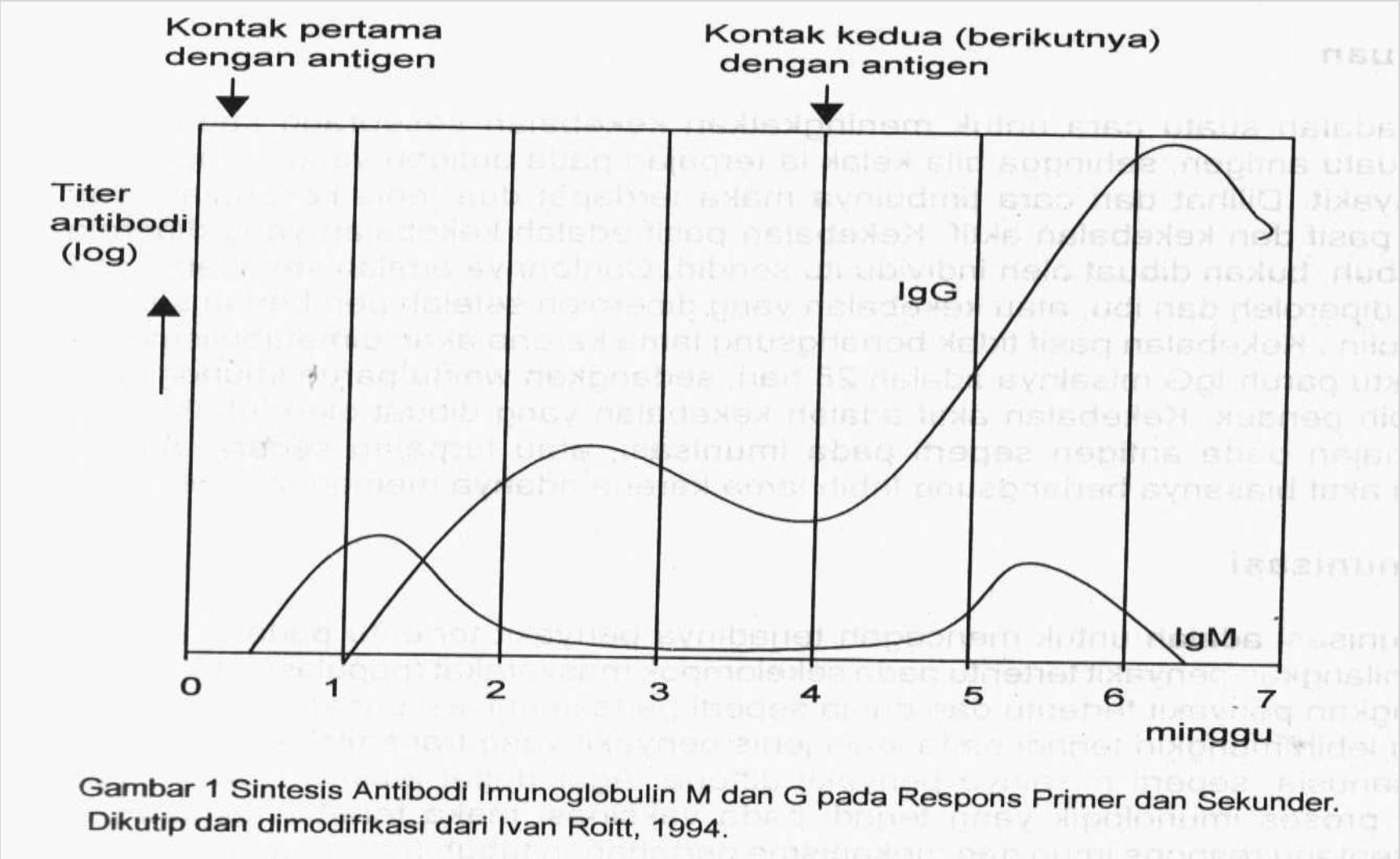
- Bila ada antigen [bakteri,virus,parasit,racun kuman] memasuki tubuh, maka tubuh akan berusaha menolaknya. Tubuh membuat zat berupa antibodi atau antitoksin.
- Reaksi tubuh terhadap Ag pertama kali berlangsung lama dan lemah. Sedangkan respon kedua dan seterusnya **tubuh lebih mengenal jenis Ag dan** mampu membentuk zat Antibodi dalam waktu singkat dengan jumlah yang banyak
- Dalam waktu tertentu jumlah berkurang, sehingga perlu imunisasi ulang

Tindakan pemberian vaksin thd seseorang disebut **IMUNISASI** atau **VAKSINASI**

- Respon imun dan memori **mirip dengan infeksi alamiah, tetapi tanpa menimbulkan penyakit** (**tinggi imunogenitas, rendah reaktogenitas**)

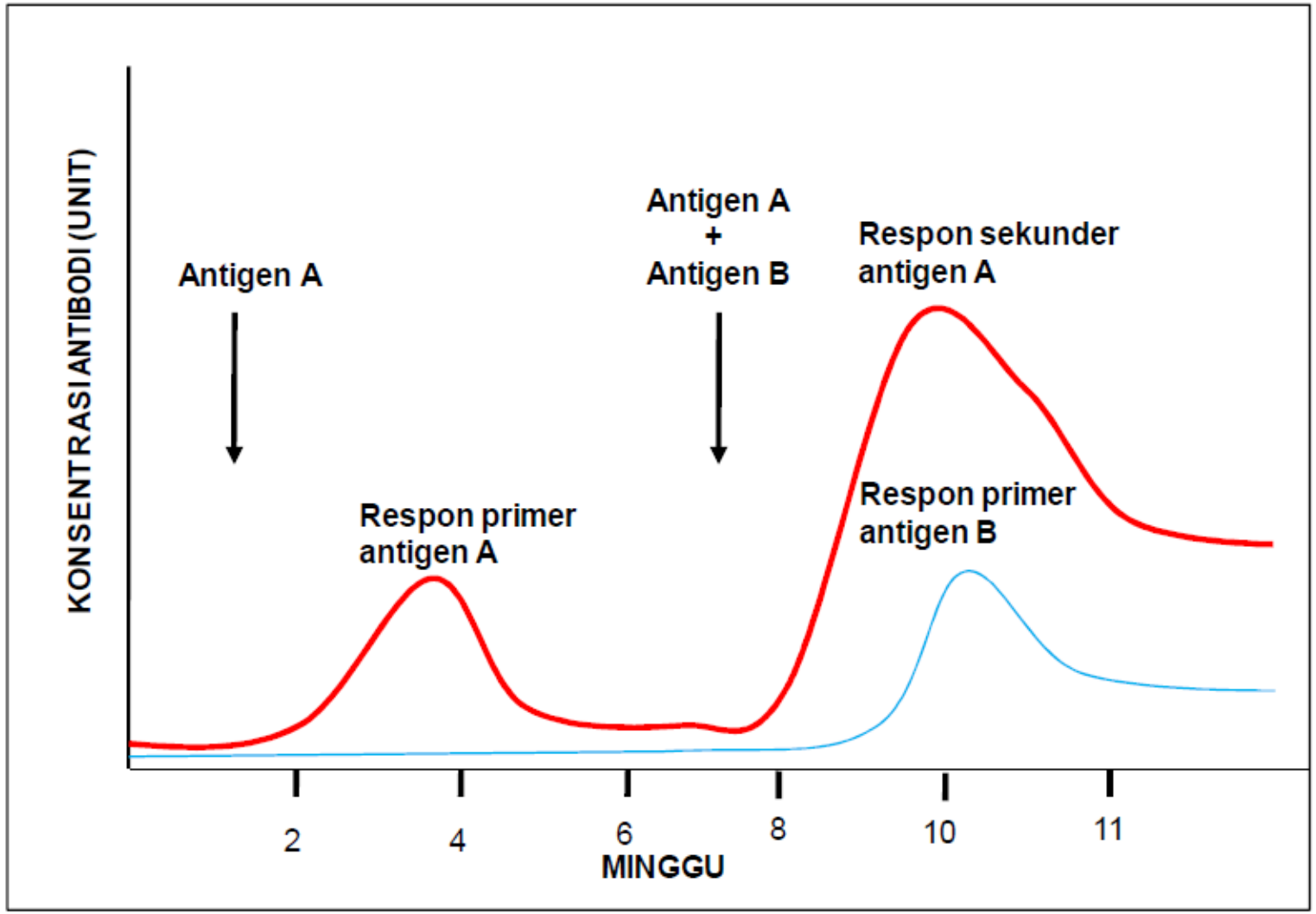
- Penyakit infeksi dapat dicegah dengan imunisasi

RESPON IMUN



Gambar 1 Sintesis Antibodi Imunoglobulin M dan G pada Respons Primer dan Sekunder. Dikutip dan dimodifikasi dari Ivan Roitt, 1994.

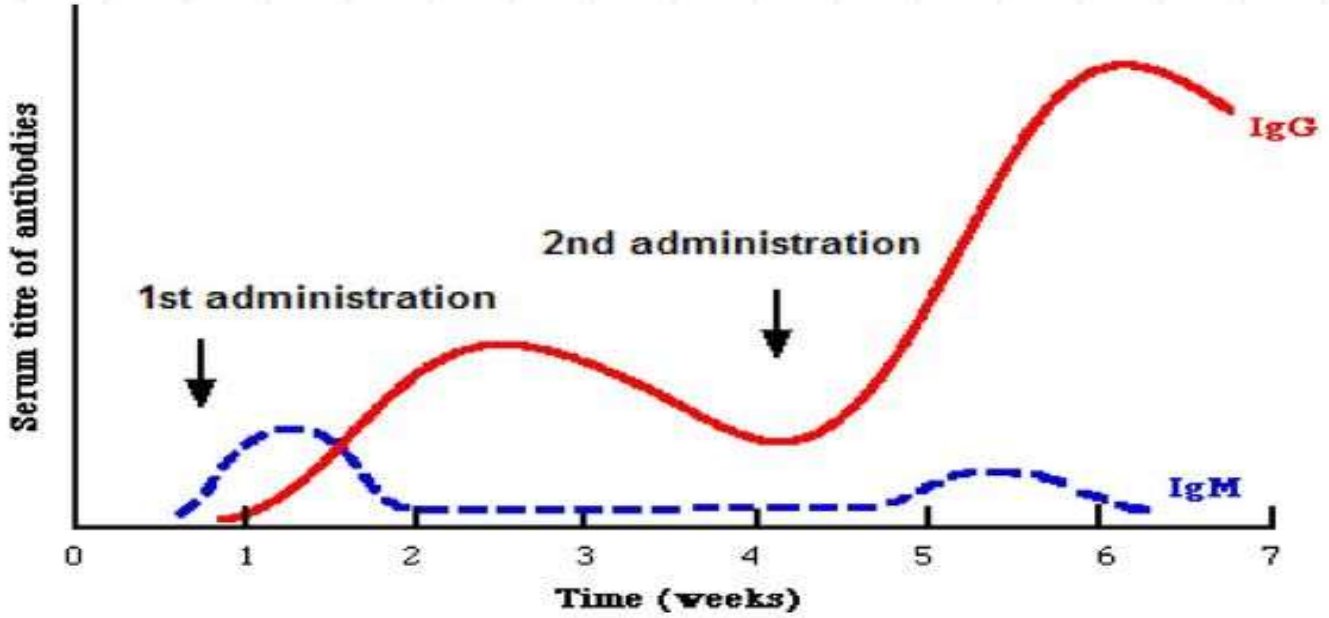
RESPON IMUN



Respon sekunder antigen A mensintesis antibody dengan konsentrasi lebih tinggi daripada respon primer antigen B

Booster

- Respon imun thd vaksin berpotensi menurun
- Diperlukan "booster", pemberian vaksin ulang utk menguatkan dan memperpanjang durasi imunitas
- Pemberian selama respon primer, akan memperlama dan memperkuat respon melawan vaksin



Vaksin Covid-19

- Perusahaan vaksin terus berupaya mengembangan vaksin Covid 19
- Dalam keadaan normal, mulai dari pembentukan rencana, mulai identifikasi antigen, pembuatan seed vaksin, prototype vaccine sampai kepada tahapan pre-klinik dan uji klinik memerlukan waktu 10-15 th
- Pada kondisi pandemia hal ini dipercepat
- Per 20 Agustus 2020: ada 30 kandidat vaksin dalam tahap evaluasi klinik, dan 169 dalam evaluasi tahap preklinik

Major Steps in vaccine development

Actions taken to ensure a new vaccine is safe and works well

R&D
Platform Choice , Design 1-5 targets, Prepare small batches, Invitro testing, Target selection

Pre-clinical studies
Vaccine is tested in animal studies for efficacy and safety, including challenge studies

Phase I clinical trial
Small groups of healthy adult volunteers receive the vaccine to test for safety

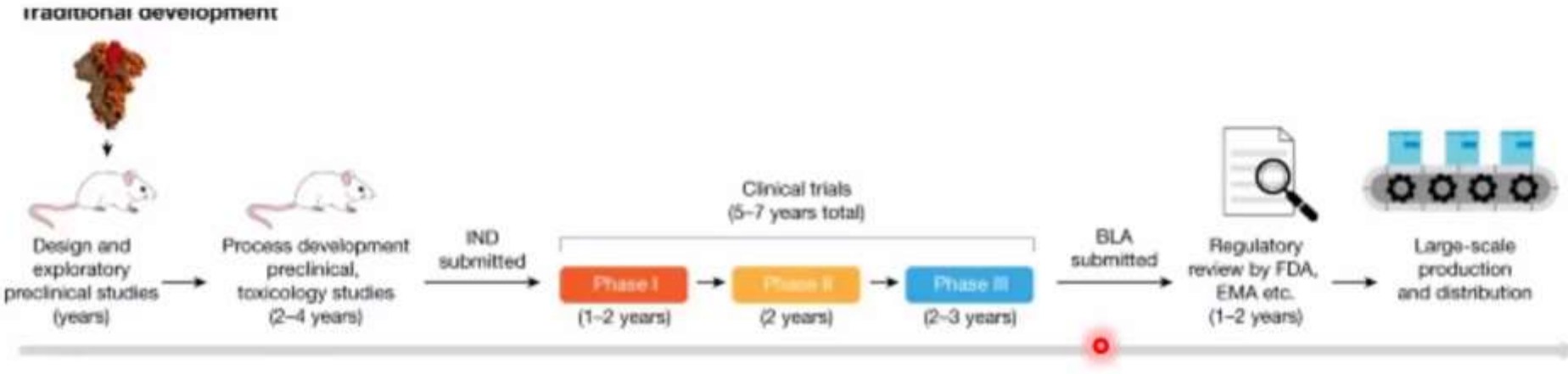
Phase II clinical trial
Vaccine is given to people who have characteristics (such as age and physical health) similar to those for whom the new vaccine is intended

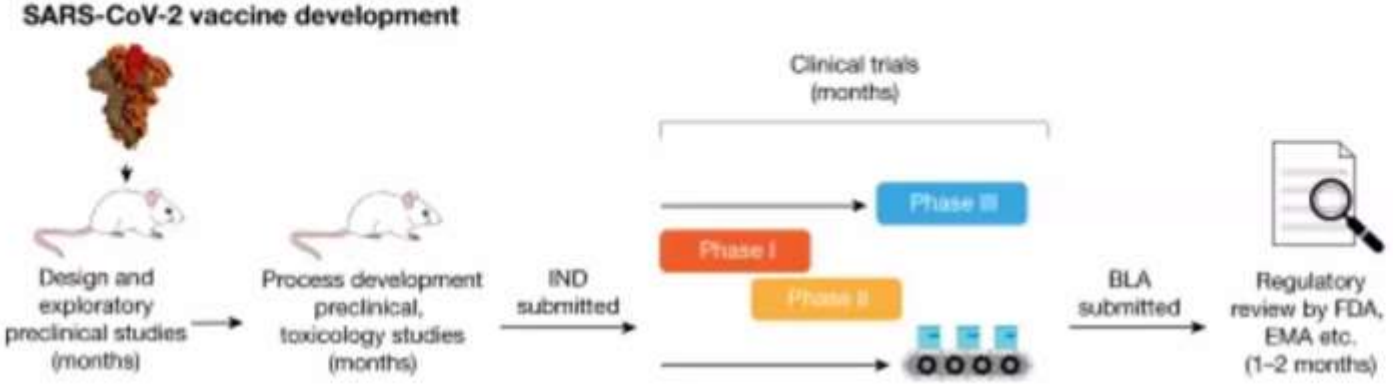
Phase III clinical trial
Vaccine is given to thousands of people and tested for efficacy and safety

Phase IV post marketing surveillance
Ongoing studies after the vaccine is approved and licensed, to monitor adverse events and to study long-term effects of the vaccine in the

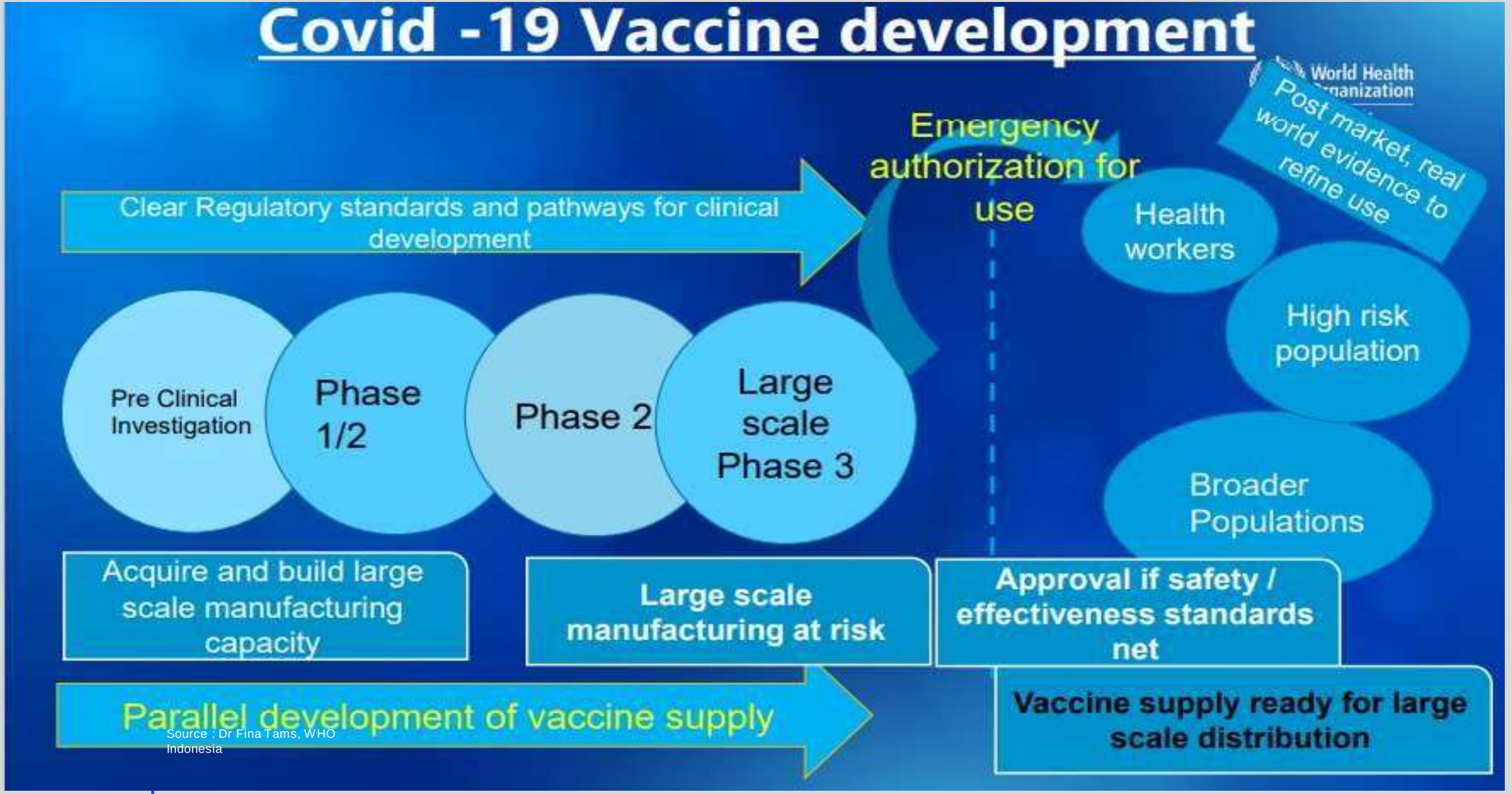
Amin Subandrio, PIT PAMKI 2020

Traditional and accelerated vaccine-development pipelines

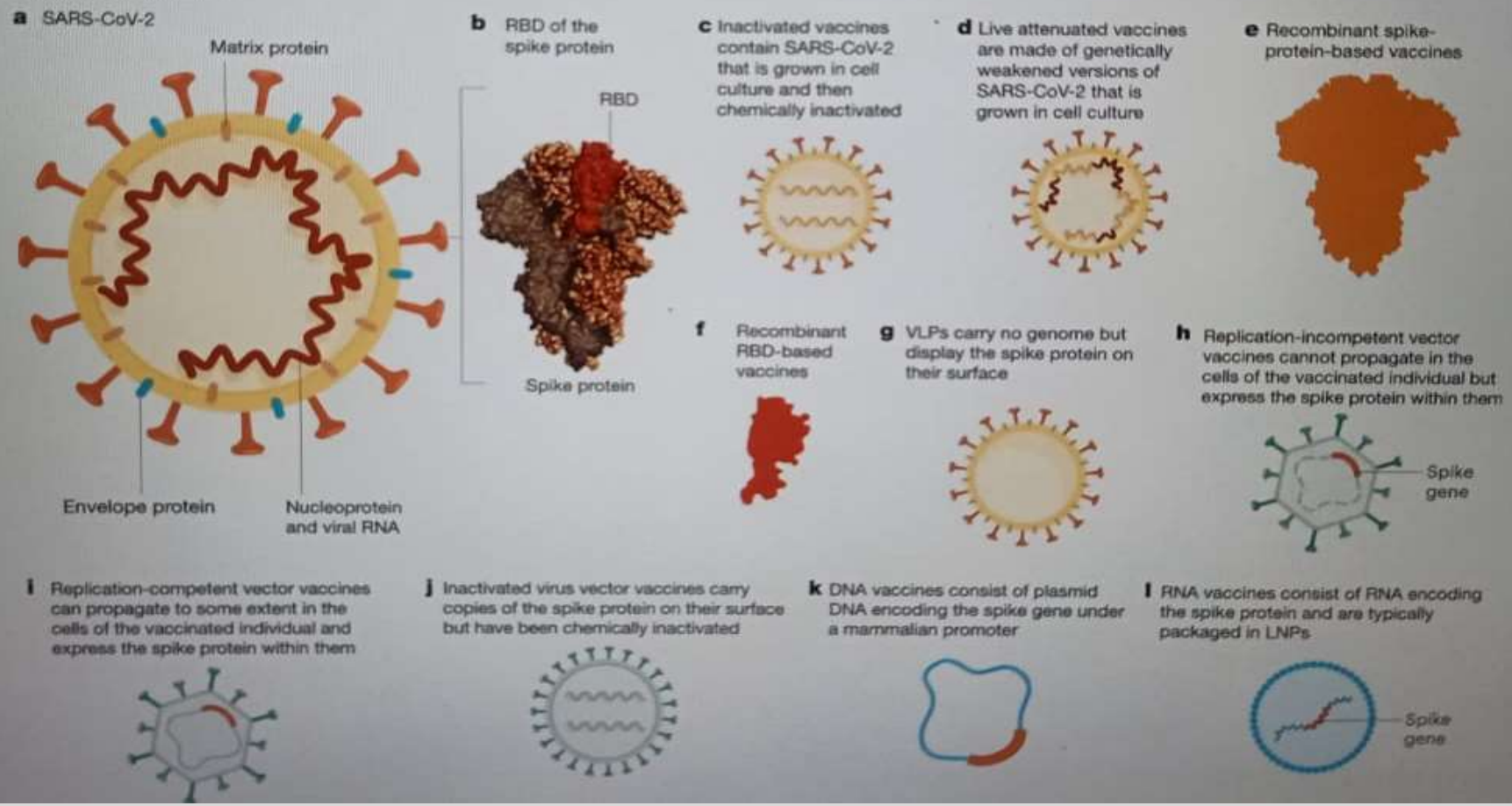




Amin Subandrio, PIT PAMKI 2020

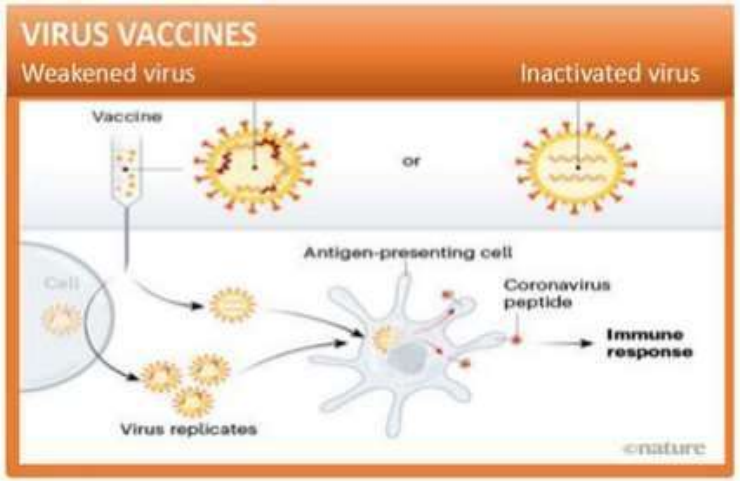

Covid -19 Vaccine development
World Health Organization
Post market, real world evidence to refine use
Emergency authorization for use
Clear Regulatory standards and pathways for clinical development
Health workers
High risk population
Broader Populations
Pre Clinical Investigation
Phase 1/2
Phase 2
Large scale Phase 3
Acquire and build large scale manufacturing capacity
Large scale manufacturing at risk
Approval if safety / effectiveness standards net
Parallel development of vaccine supply
Vaccine supply ready for large scale distribution
Source : Dr Fina Tams, WHO Indonesia

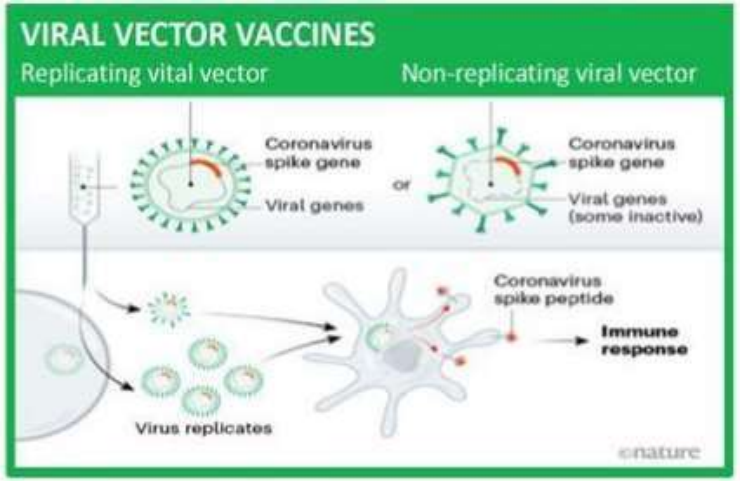
Which Vaccine platforms

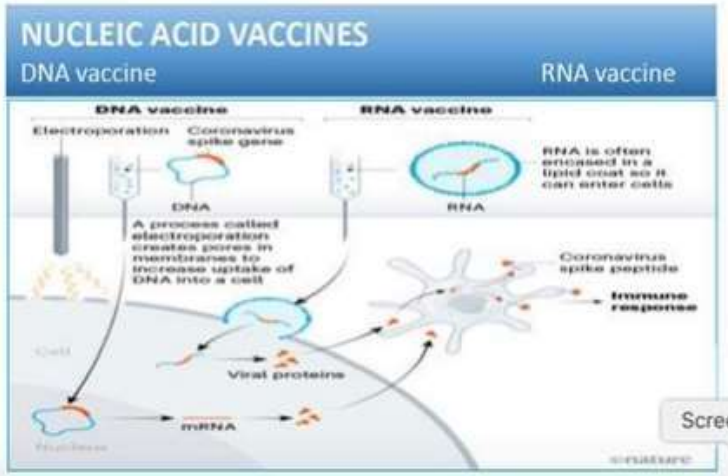


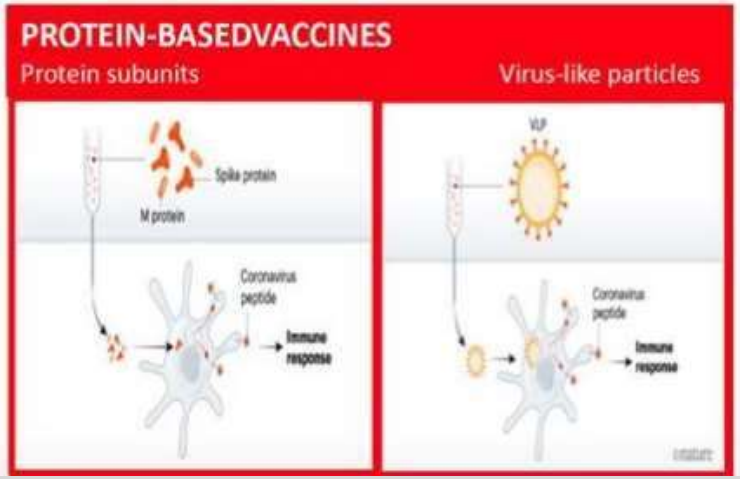
Amin Subandrio, PIT PAMKI 2020

Platform teknologi vaksin COVID-19









Screenshot

Kandidat Kuat Vaksin COVID 19

- Pfizer/ Fosum Pharma Biontech (mRNA)
- Moderna (mRNA)
- Oxford/ Astrazeneca (Viral vector)
- Sinovac (Inactivated virus)
- Novavax (Protein virus)

Vaksin mRNA

- Messenger RNA(mRNA), adalah **kode sintetik mRNA serupa dengan mRNA virus** → membentuk **protein spike** → membentuk kekebalan tubuh
- Teknologi terbaru, secara teori sangat aman
- mRNA sintetik yang dimasukkan tidak akan masuk ke nukleus sehingga **tidak akan mengubah DNA manusia**, setelah vaksin selesai mengkode maka akan dihancurkan oleh tubuh

Vaksin Viral Vector

Menggunakan **vektor virus lain** yang diberikan **protein spike SARC COV 2** → mampu "menginfeksi" seseorang tanpa menyebabkan penyakit

Virus lain bereran sebagai vektor untuk membawa protein ke sel target → **mampu memicu respon imun**

Keuntungan

- Dapat memasukkan gen yang sangat spesifik ke sel host dengan respon imun yang baik
- **Terhindar dari partikel infeksius apapun pada virus**
- Telah digunakan secara luas untuk MERS-CoV dengan hasil yang bagus

Keterbatasan

- Sel host **mungkin yang telah memiliki imunitas** terhadap vector karena infeksi sebelumnya, sehingga efikasi akan berkurang
- Dapat memicu kanker karena integrasi genome virus ke genome host

Baxter D. Active and passive immunity, vaccine types, excipients and licensing. Occup Med. 2007 Dec 1;57(8):552–6.
Kaur SP, Gupta V. COVID-19 Vaccine: A comprehensive status report. Virus Res. 2020 Oct;288:198114.

INACTIVATED VACCINE

- Dasar pengembangan vaksin yang sejak lama, (sebagai ***the most traditional vaccine approach***)
- telah dilakukan beberapa puluh tahun
- menyuntik seseorang dengan virus yang dimatikan (*inactivated vaccine*)
- tidak akan menyebabkan infeksi serius.
- (sudah banyak dipakai untuk pembuatan vaksin seperti influenza dan polio).

Vaksin Protein Subunit / Purified Antigen

Pembuatan

- Seperti ***inactivated whole cell vaccines***, namun hanya **mengandung bagian dari pathogen** (protein spike) yang **dapat memicu respon imun saja**

Respon Imun

- Dalam pembuatan **harus ditentukan kombinasi antigen yang dapat memicu respon imun** (lebih sulit)
- Respon imun dapat terbentuk, namun **tidak ada jaminan bahwa sel memori akan terbentuk**

"Excellent stability profile, but less strong immune response compared to live attenuated vaccines"
Tidak mengandung komponen hidup, sehingga tidak ada risiko menyebabkan penyakit

Baxter D. Active and passive immunity, vaccine types, excipients and licensing. Occup Med. 2007 Dec 1;57(8):552–6.
Kaur SP, Gupta V. COVID-19 Vaccine: A comprehensive status report. Virus Res. 2020 Oct;288:198114.

Perbandingan berbagai platform teknologi vaksin COVID-19

Types of Vaccines	Inactivated	Live attenuated	DNA and RNA	Viral Vector	Subunit	Virus-like particles
How it works	An inactivated vaccine uses the whole virus after it has been killed with heat or chemicals	This is a weakened version of the actual virus.	This vaccines uses DNA or RNA molecules to teach the immune system to target key viral proteins	This approach takes a harmless virus and uses it to deliver viral genes to build immunity.	This vaccine uses a piece of a virus' surface to focus your immune system on a single target.	This vaccine uses molecules that closely resemble viruses, but are non-infectious because they contain no viral genetic material, to elicit an immune response

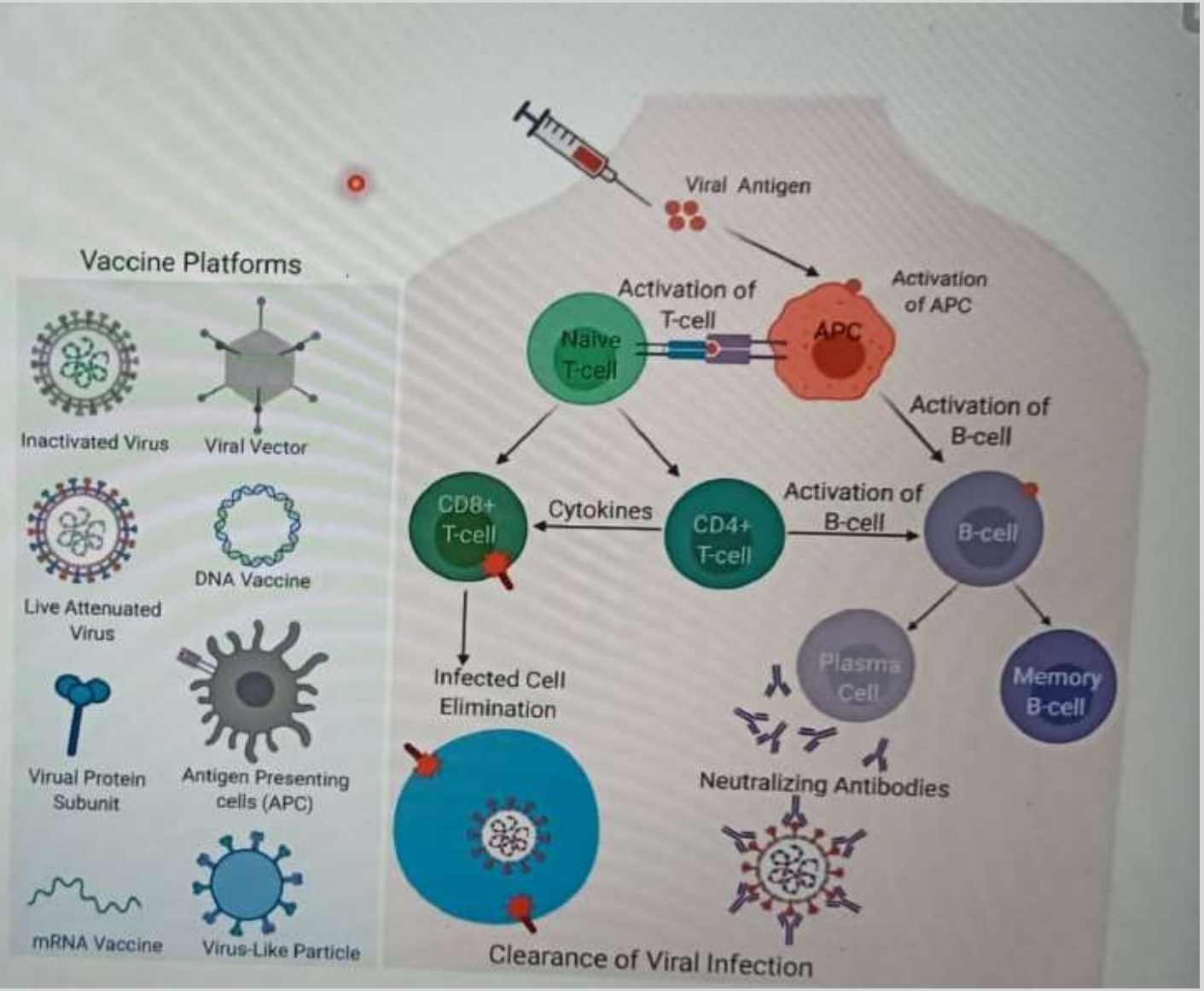
Perbandingan berbagai platform teknologi vaksin COVID-19

Types of Vaccines	Inactivated	Live attenuated	DNA and RNA	Viral Vector	Subunit	Virus-like particles
Disadvantages	Not as effective as a live virus. Some previous inactivated vaccines have made the disease worse; safety for the novel coronavirus needs to be shown in clinical trials	May not be safe for those with compromised immune systems.	Never been done before. There are no licensed DNA or RNA vaccines currently in use	Important to pick a viral vector that is truly safe. An immune response to the viral vector could make the vaccine less effective.	May not stimulate a strong response; other chemicals may need to be added to boost long-term immunity	May not stimulate a strong response and may need booster shots to get ongoing protection against diseases.

Perbandingan berbagai platform teknologi vaksin COVID-19

Types of Vaccines	Inactivated	Live attenuated	DNA and RNA	Viral Vector	Subunit	Virus-like particles
Advantages	Generally safe because the virus is already dead and is easy to make.	Stimulates a robust immune response without causing serious disease.	Easy and quick to design	Live viruses tend to elicit stronger immune responses than dead viruses or subunit vaccines.	Focusses the immune response on the most important part of the virus for protection and cannot cause infection.	Lack the viral genome, potentially yielding safer and cheaper vaccine candidates

Immune Response to Vaccine



Amin Subandrio, PIT PAMKI 2020

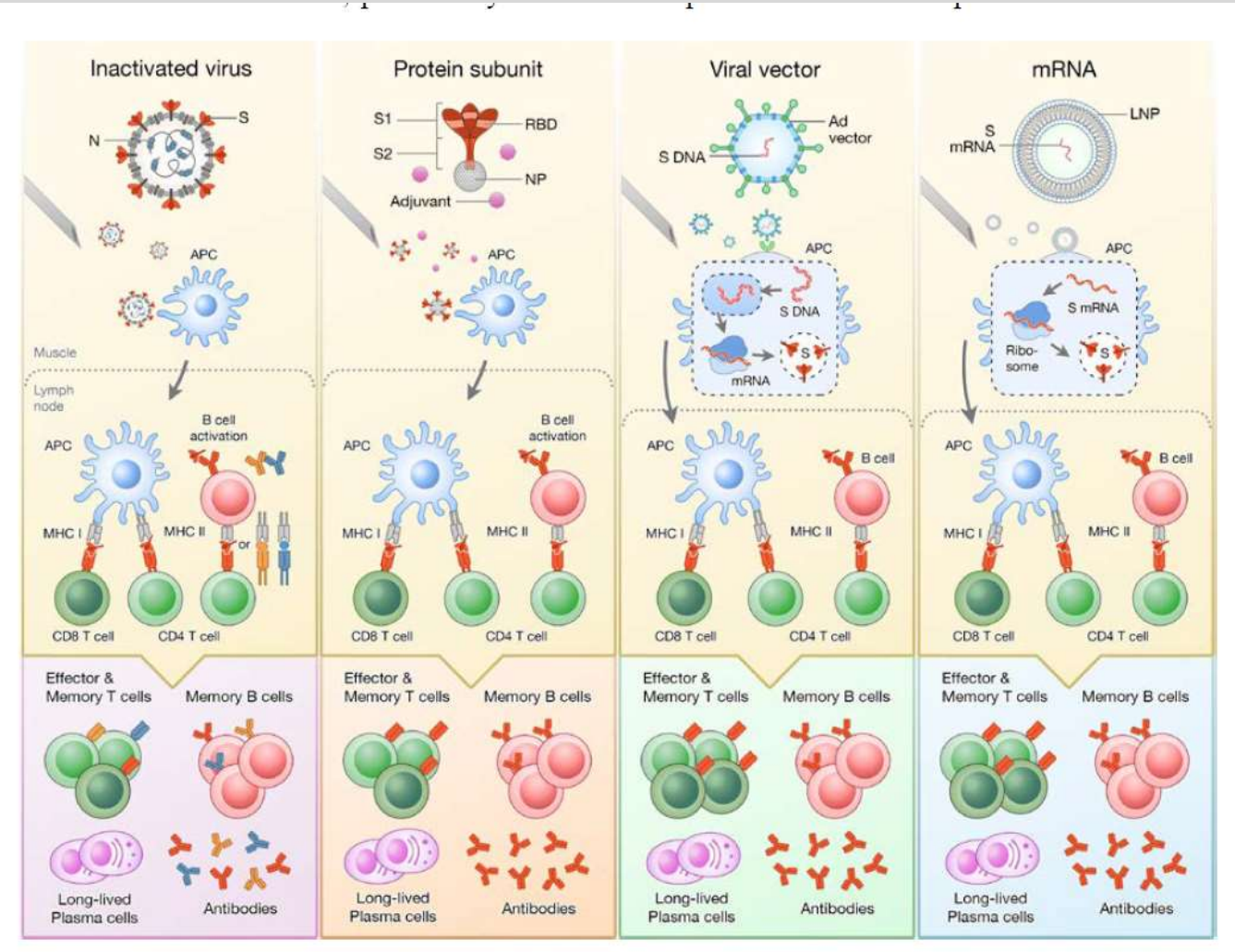


Figure 2. Comparison In Immunogenesis Of Each Vaccine Modalities And Natural Infection Platform

Youdiil Ophinni, et all, 2020

Table 2. Efficacy Characteristic and Details on Phase 3 Trial of Each Vaccine Candidate.

Manufacturer	Current trial phase	Phase 3 trial location	Sample size	Subject age	Vaccine efficacy	Subgroup efficacy analysis	Safety concern
BioNTech/Pfizer	3 (completed)	US, Germany, Turkey, South Africa, Brazil, Argentina	43,548	16 years or older (including >55 years)	95% (all participants)	16-55 years:95,6% ≥ 55 years:93,7% ≥ 65 years: 94,7% ≥ 75 years: 100%	Anaphylactoid reaction (post-licensure)
Moderna	3 (completed)	US	>30,000	18 years or older (including >55 years)	94.5% (all participants)	18-<65: 93,4% ≥ 65 : 100%	ND
University of Oxford/ AstraZeneca	3 (interim)	UK, US, South Africa, Colombia, Peru, Argentina	40,000	18 years or older (including >55 years)	90.0% (LD/ SD) 62.1% (SD/ SD)	ND	Transverse myelitis (n=1)
Gamaleya	3 (interim)	Russia, UAE, Belarusia, India, Venezuela	>20,000	18-60 years	91.4%	N/A	ND
Novavax	3 (ongoing)	UK, India, South Africa, Mexico	15,000 (UK)	18-59 years*	ND	ND	ND
Janssen/ Johnson & Johnson	3 (ongoing)	US, Argentina, Chile, Colombia, Mexico, South Africa, Philippines	60,000	18 years or older (including >55 years)*	ND	ND	ND
Sinovac	3 (ongoing)	China, Indonesia, Brazil, Turkey, Chile	>30,000	18-59 years*	91.25% (Turkey)	N/A	ND
Sinopharm	3 (ongoing)	China, UAE, Morocco, Egypt, Bahrain, Jordan, Pakistan, Peru, Argentina	31,000	18-59 years*	86% (UAE)	N/A	ND
CanSino	3 (ongoing)	China, Pakistan, Argentina, Chile, Mexico, Russia	40,000	18 years or older (including >55 years)*	ND	ND	ND

* Based on phase 2 clinical trials; LD/SD, low dose/standard dose; SD/SD, standard dose/standard dose; N/A, not available; ND, no data.

Youdiil Ophinni, et all, 2020

Table 3. Efficiency Characteristics of Each Vaccine Candidate.

Manufacturer	Doses	Storage	Dosing schedule	Price per dose	Global pre-order estimate (billions)	Production capacity target/year, by end of 2021 (billions)
BioNTech/Pfizer	30 ug	-70°C 2-8°C (5 days)	0.21 days	$19.5	1.1	1.3
Moderna	100 ug**	-20°C 2-8°C (1 month)	0.28 days**	$37	0.8	0.5
University of Oxford/ AstraZeneca	0.22 ml or 0.5 ml**	2-8°C	0.28 days**	$2-$5	3.2	3
Gamaleya	0.5 ml or 1.0 ml**	-18°C (frozen type); 2-8°C (lyophilized)	0.21 days**	$10	0.5	0.5
Novavax	5 ug or 25 ug*	2-8°C	0.21 days*	$16	1.4	2
Janssen/Johnson & Johnson	1 ml*	-20°C 2-8°C (3 months)	0 (single shot) or 0.56 days*	$10	1.3	1
Sinovac	3 ug or 6ug*	2-8°C	0.14 or 0.28*	$30	0.2	0.6
Sinopharm	4 ug or 8 ug*	2-8°C	0.21 days	$72.5	0.1	1
Cansino	1 ml*	ND	0 day (single shot)*	ND	ND	ND

* Based on phase 2 clinical trials. ** Based on phase 3 clinical trials interim report. ND, no data.

Youdiil Ophinni, et all, 2020

Mengapa Vaksin Merah Putih?

Dikembangkan

- Menggunakan virus COVID-19 yang bersirkulasi di Indonesia
- di Institusi Penelitian Indonesia
- Oleh Peneliti2 muda Indonesia
- Untuk melindungi rakyat Indonesia dari COVID-19

Vaksin Merah-Putih

REC

Sumber: Kemenristek/BRIN

Eijkman	LIPI	UI	ITB	UNAIR	UGM
Progres: Kloning gen spike ke dalam ekspresi yeast Diperkirakan Juli 2021 seed vaccine sudah dapat diproduksi skala masal oleh PT Bio Farma	Progres: Kloning plasmid rekombinan ke dalam Escherichia coli Diperkirakan Mei 2021 sudah dilakukan pengolahan data, pelaporan dan draf paten	Progres: Imunisasi Vaksin DNA hewan coba dan transkripsi *in vitro* vaksin RNA Diperkirakan Juni 2021 pembuatan sel CHO pengekspresi vaksin subunit rekombinan dan vaksin VLP	Progres: Subkloning plasmid antara Diperkirakan Desember 2021 telah dilakukan uji imunogenisitas pada mencit	Progres: Konstruksi vektor adenovirus dan receptor binding domain (RBD) Diperkirakan Februari 2021 baru akan dilakukan produksi synthetic adenovirus	Progres: Integrasi DNA sintetik ke dalam vektor plasmid Diperkirakan tahun kedua riset dilakukan uji imunogenisitas pada hewan uji mencit a

Motto Vaksin Merah-Putih

- Virus berasal dari Indonesia
- Dikembangkan oleh peneliti Indonesia
- Diproduksi oleh produsenvaksin di Indonesia
- Dipersembahkan untuk masyarakat Indonesia

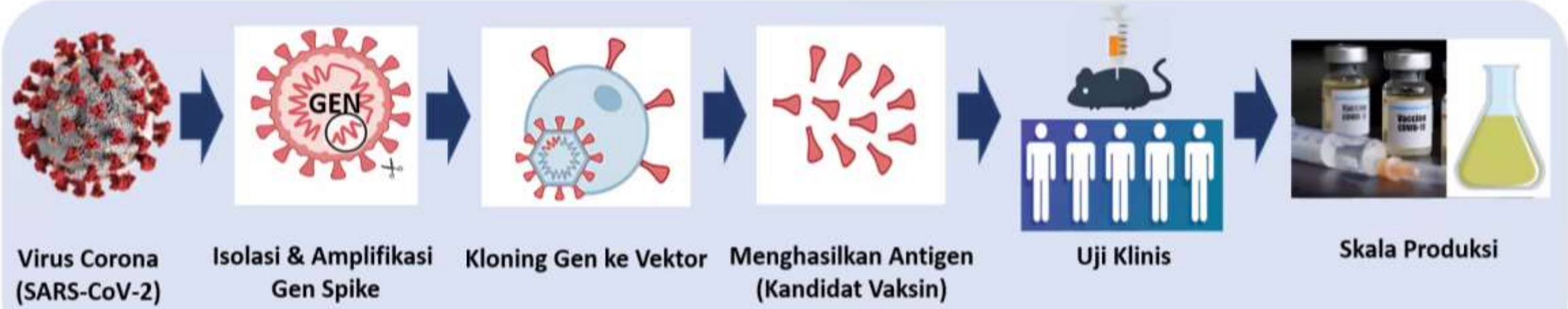
RISTEK-BRIN EIJKMAN

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

bioFarma

Vaksin COVID-19

PENGEMBANGAN VAKSIN COVID-19 MENGGUNAKAN ISOLAT VIRUS INDONESIA: PRODUKSI *SEED VACCINE* COVID-19



Virus Indonesia	PCR Analisa Gen Ekspresi Protein	Kloning Transfeksi Sel Mammalia	Ekspresi Protein Uji Imunologi Seed Vaccine	Uji Klinik Hewan Coba (In-Vivo) & Manusia	Skala Produksi Vaksin

LBM EIJKMAN dan KONSORSIUM

LEMBAGA BIOLOGI MOLEKULER EIJKMAN

Amin Subandrio, PIT PAMKI 2020

Wassalamu'alaikum Wr.Wb.