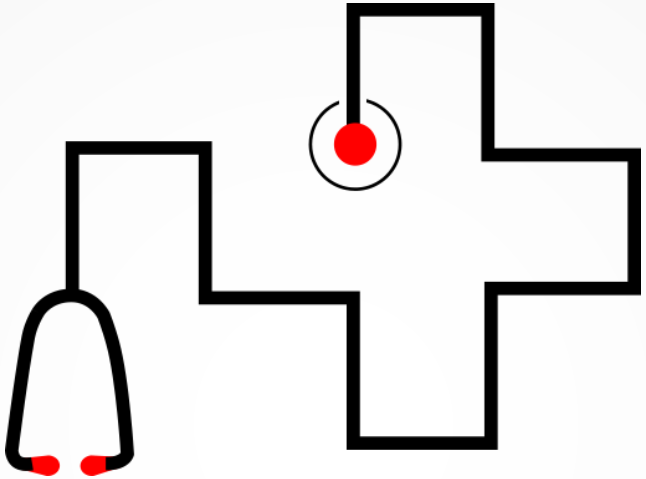


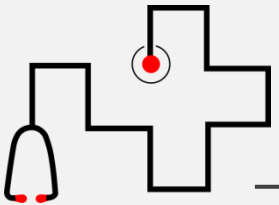
MATERI 5 (FA 1604)

PENYAKIT INFEKSI DAN VAKSIN

Disusun oleh :
Umi Baroroh, S.Si., M.Biotek.
Sekolah Tinggi Farmasi Indonesia

PENYAKIT INFEKSI

Penyakit yang disebabkan karena masuknya bibit penyakit. Penyebab utama infeksi adalah bakteri, virus, parasit, dan jamur. Organisme tersebut menyebar dengan berbagai cara dan bantuan vektor sehingga dapat menular dari satu orang ke orang lain.

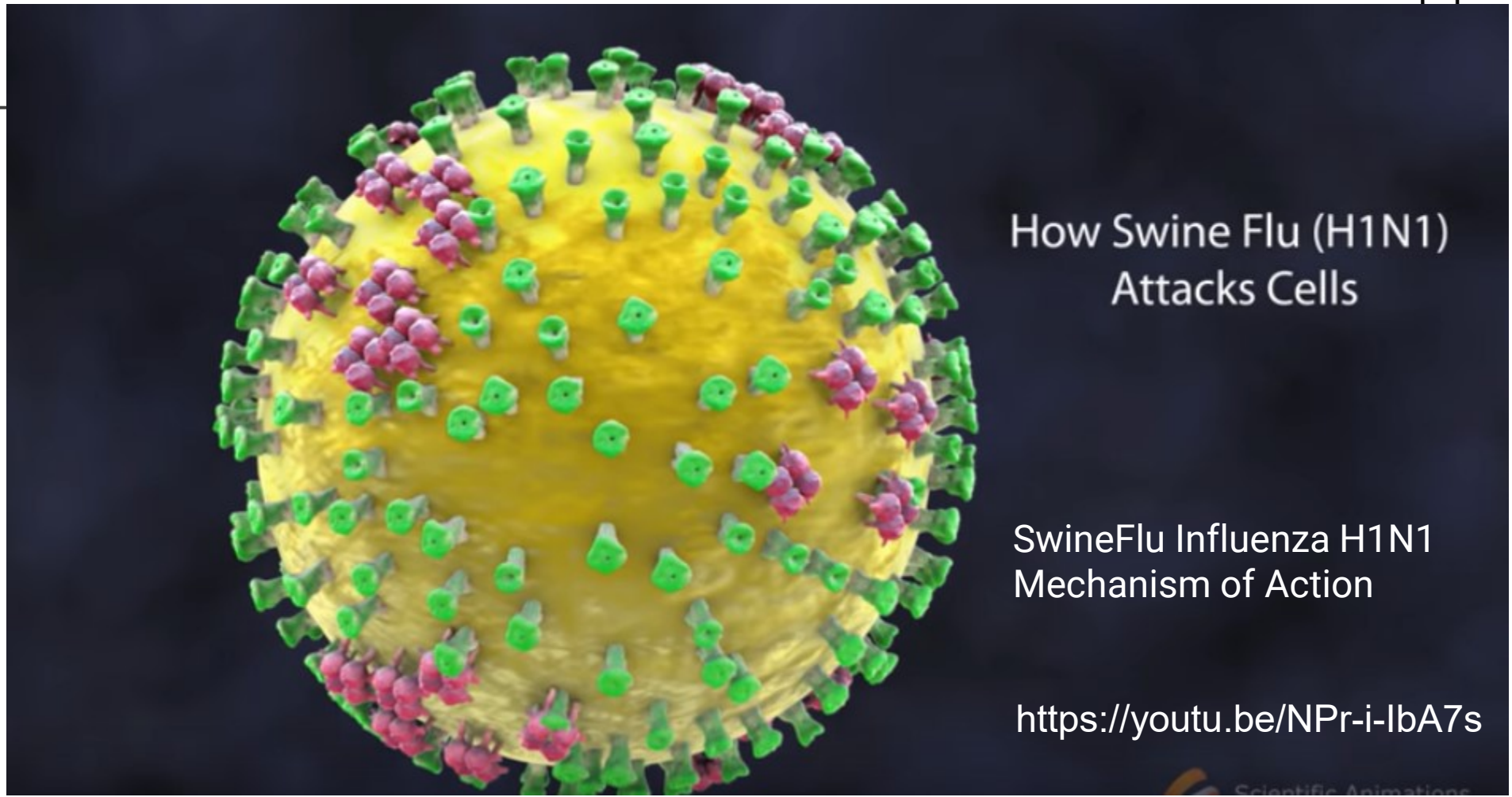


RUTE INFEKSI PATOGEN

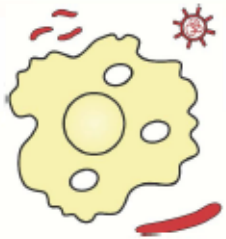
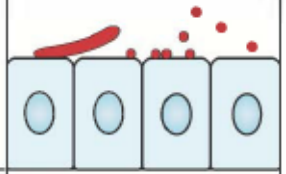
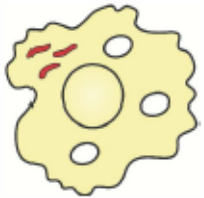
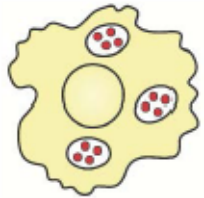
Mulut dan saluran pernapasan
Transmisi : Terhirup dan tertelan materi non-efektif (droplet), spora
Contoh : Influenza, *B.anthracis*

Saluran pencernaan
Transmisi : Makanan/air terkontaminasi
Contoh : Hepatitis A (Jaundice), *Salmonella typhi* (Typhoid)

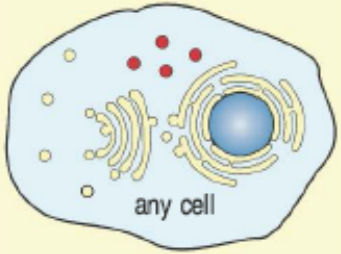
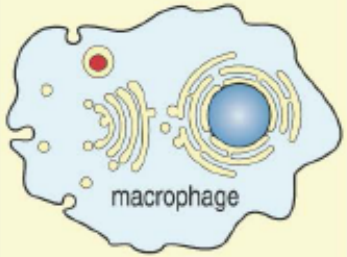
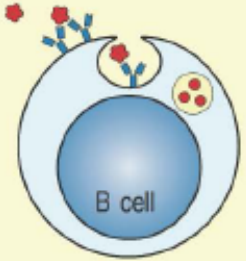
Saluran reproduksi dan lainnya
Transmisi : Seksual, darah terkontaminasi
Contoh : Hepatitis B, HIV (AIDS), *Treponema palidum* (Syphilis)


How Swine Flu (H1N1)
Attacks Cells
SwineFlu Influenza H1N1
Mechanism of Action
https://youtu.be/NPr-i-IbA7s

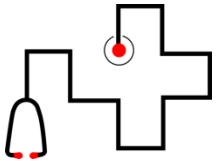
RESPON TERHADAP PENYAKIT

	Extracellular		Intracellular	
	Interstitial spaces, blood, lymph	Epithelial surfaces	Cytoplasmic	Vesicular
Site of infection				
Organisms	Viruses Bacteria Protozoa Fungi Worms	*Neisseria gonorrhoeae* *Streptococcus pneumoniae* *Vibrio cholerae* *Helicobacter pylori* *Candida albicans* Worms	Viruses *Chlamydia* spp. *Rickettsia* spp. Protozoa	*Mycobacterium* spp. *Yersinia pestis* *Legionella pneumophila* *Cryptococcus neoformans* *Leishmania* spp.
Protective immunity	Complement Phagocytosis Antibodies	Antimicrobial peptides Antibodies, especially IgA	NK cells Cytotoxic T cells	T-cell and NK-cell dependent macrophage activation

RESPON TERHADAP PENYAKIT

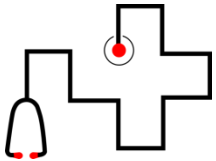
	Cytosolic pathogens	Intravesicular pathogens	Extracellular pathogens and toxins
			
Degraded in	Cytosol	Endocytic vesicles (low pH)	Endocytic vesicles (low pH)
Peptides bind to	MHC class I	MHC class II	MHC class II
Presented to	Effector CD8 T cells	Effector CD4 T cells	Effector CD4 T cells
Effect on presenting cell	Cell death	Activation to kill intravesicular bacteria and parasites	Activation of B cells to secrete Ig to eliminate extracellular bacteria/toxins

IMUNITAS HUMORAL



- Diperantarai oleh antibodi yang disekresikan oleh sel B → pengikatan antigen dengan imunoglobulin permukaan (BCR)
- Semua globulin serum dengan aktivitas antibodi dinamakan imunoglobulin :
  1. Mengenal dan mengikat epitop
  2. Menampilkan fungsi biologik setelah berkombinasi dengan antigen
- Reaksi antara antigen-antibodi mengaktifkan sistem komplemen

IMUNITAS SELULER



- Diperantarai sel T
- Setiap sel T mengekspresikan beberapa reseptor antigen yang identik → T cell receptor (TCR) sehingga memiliki berbagai fungsi :

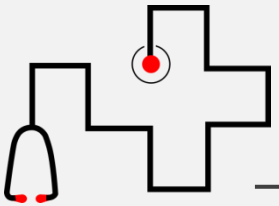
1. Bekerja sama dengan sel B → melepaskan berbagai sitokin untuk aktivasi sel B sehingga meningkatkan produksi antiodi (Th)
2. Efek inflamatori → melepaskan sitokin yang menginduksi migrasi dan aktivasi monosit dan makrofag yang menyebabkan reaksi inflamatory *delayed-type hypersensitivity* (Tdth)
3. Efek sitotoksik → menyebabkan kematian sel target (Tc)
4. Efek regulator → Sel Th1 dan Th2 saling meregulasi dengan efek negatif atau T regulator (Treg)
5. Sinyal melalui sitokin → secara langsung atau tidak langsung sel T berkomunikasi dengan berbagai tipe sel

INFEKSI VIRUS

- Virus adalah segmen kecil asam nukleat dengan protein atau lipoprotein yang membutuhkan inang untuk replikasi.

- Virus masuk ke dalam sel melalui reseptor permukaan sel yang memiliki afinitas dan mengintegrasikan asam nukleatnya sehingga ikut dalam biosintesis sel untuk mereplikasi semua komponennya

- Respon bawaan terhadap infeksi virus diawali oleh pengenalan PAMP yang mengarah pada induksi efektor antivirus



Viruses	DNA viruses	Adenoviruses	Human adenoviruses (e.g., types 3, 4, and 7)
		Herpesviruses	Herpes simplex, varicella zoster, Epstein–Barr virus, cytomegalovirus, HHV8
		Poxviruses	Variola, vaccinia virus
		Parvoviruses	Human parvovirus
		Papovaviruses	Papilloma virus
		Hepadnaviruses	Hepatitis B virus
	RNA viruses	Orthomyxoviruses	Influenza virus
		Paramyxoviruses	Mumps, measles, respiratory syncytial virus
		Coronaviruses	Cold viruses, SARS
		Picornaviruses	Polio, coxsackie, hepatitis A, rhinovirus
		Reoviruses	Rotavirus, reovirus
		Togaviruses	Rubella, arthropod-borne encephalitis
		Flaviviruses	Arthropod-borne viruses, (yellow fever, dengue fever)
		Arenaviruses	Lymphocytic choriomeningitis, Lassa fever
		Rhabdoviruses	Rabies
		Retroviruses	Human T-cell leukemia virus, HIV

Figure 2-2 part 1 of 3 Immunobiology, 7ed. (© Garland Science 2008)

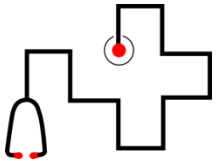
VIRUS MANUSIA

MEKANISME RESPON TERHADAP VIRUS

TABLE 17-1 Mechanisms of humoral and cell-mediated immune responses to viruses

Response type	Effector molecule or cell	Activity
Humoral	Antibody (especially secretory IgA)	Blocks binding of virus to host cells, thus preventing infection or reinfection
	IgG, IgM, and IgA antibody	Blocks fusion of viral envelope with host cell's plasma membrane
	IgG and IgM antibody	Enhances phagocytosis of viral particles (opsonization)
	IgM antibody	Agglutinates viral particles
	Complement activated by IgG or IgM antibody	Mediates opsonization by C3b and lysis of enveloped viral particles by membrane-attack complex
Cell mediated	IFN-λ secreted by T_H or T_C cells	Has direct antiviral activity
	Cytotoxic T lymphocytes (CTLs)	Kill virus-infected self cells
	NK cells and macrophages	Kill virus-infected cells by antibody-dependent cell-mediated cytotoxicity (ADCC)

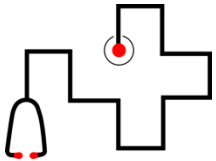
INFEKSI BAKTERI



•Bergantung pada jumlah organisme yang masuk dan faktor virulensinya, serta tingkat ketahanan tubuh inang.

•Pada beberapa infeksi bakteri, gejala penyakit disebabkan bukan oleh patogen itu sendiri tetapi oleh respon imun, misalnya produksi sitokin yang berlebihan ketika induksi sel Th

INFEKSI BAKTERI



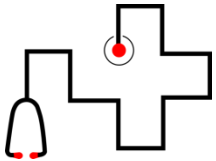
- Bakteri ekstraseluler menginduksi produksi antibodi
- Bakteri ekstraseluler dapat bersifat patogen karena mereka menginduksi respons peradangan lokal atau menghasilkan racun.
- Kekebalan bawaan tidak terlalu efektif terhadap bakteri intraseluler
- Bakteri intraseluler dapat mengaktifkan sel NK sebagai pertahanan awal

MEKANISME RESPON TERHADAP BAKTERI

TABLE 17-3 Host immune responses to bacterial infection and bacterial evasion mechanisms

Infection process	Host defense	Bacterial evasion mechanisms
Attachment to host cells	Blockage of attachment by secretory IgA antibodies	Secretion of proteases that cleave secretory IgA dimers (*Neisseria meningitidis, N. gonorrhoeae, Haemophilus influenzae*) Antigenic variation in attachment structures (pili of *N. gonorrhoeae*)
Proliferation	Phagocytosis (Ab- and C3b-mediated opsonization)	Production of surface structures (polysaccharide capsule, M protein, fibrin coat) that inhibit phagocytic cells Mechanisms for surviving within phagocytic cells Induction of apoptosis in macrophages (*Shigella flexneri*)
	Complement-mediated lysis and localized inflammatory response	Generalized resistance of gram-positive bacteria to complement-mediated lysis Insertion of membrane-attack complex prevented by long side chain in cell-wall LPS (some gram-negative bacteria)
Invasion of host tissues	Ab-mediated agglutination	Secretion of elastase that inactivates C3a and C5a (*Pseudomonas*)
Toxin-induced damage to host cells	Neutralization of toxin by antibody	Secretion of hyaluronidase, which enhances bacterial invasiveness

PERTAHANAN BAKTERI



Bakteri dapat menghindar dari mekanisme pertahanan inang di beberapa tahap yang berbeda :

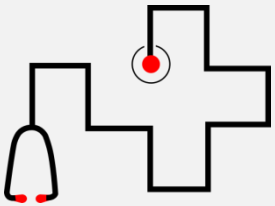
1. Perlekatan pada sel inang
2. Proliferasi
3. Invasi jaringan inang
4. Kerusakan yang diinduksi racun pada sel inang

DEFINISI VAKSIN

Menurut FI IV :

•Vaksin adalah sediaan yang mengandung zat antigenik yang mampu menimbulkan kekebalan aktif dan khas pada manusia.

•Vaksin dapat dibuat dari bakteri, riketsia atau virus dan dapat berupa suspensi organisme hidup atau inaktif atau fraksifraksinya atau toksoid.



History of vaccines

VAKSINASI/IMUNISASI

•Memasukkan ke dalam tubuh senyawa imunogenik (mikroorganisme/bagian/produknya) yang tidak berbahaya tetapi tetap memiliki determinan antigenik yang sama dengan mikroba patogen yang utuh/virulen

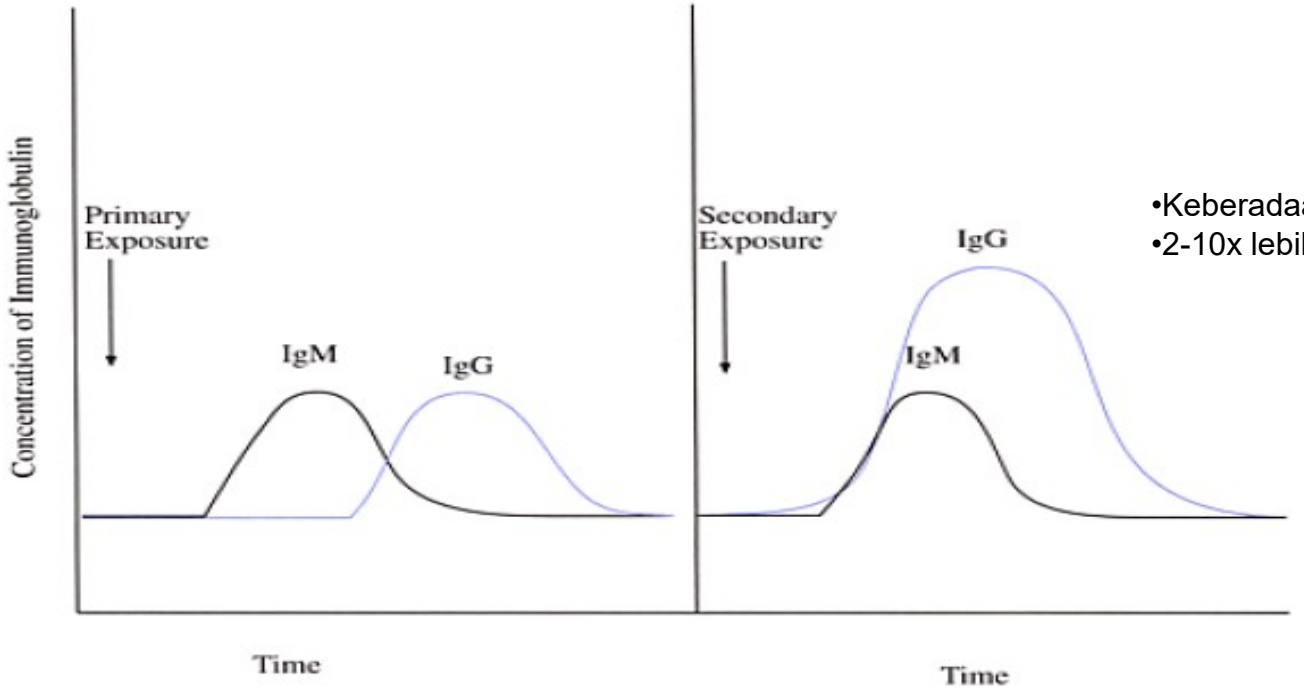
•Menginduksi sistem imun humoral atau seluler atau keduanya

Why we use vaccines

- **Vaccines can prevent infectious diseases.** Examples of vaccine-preventable diseases are: measles, polio, hepatitis B, influenza and many others.
- When most people in a community are vaccinated against a disease, the ability of the pathogen to spread is limited. This is called 'herd' or 'indirect' or 'population' immunity.
- When many people have immunity, this also indirectly protects people who cannot be vaccinated, such as very young babies and those who have compromised immune systems.

Source : WHO Presentation

RESPON PAPARAN ANTIGEN



- Keberadaan sel memori
- 2-10x lebih tinggi

KARAKTERISTIK VAKSIN IDEAL

Features of effective vaccines	
Safe	Vaccine must not itself cause illness or death
Protective	Vaccine must protect against illness resulting from exposure to live pathogen
Gives sustained protection	Protection against illness must last for several years

Figure 14-23 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Features of effective vaccines	
Induces neutralizing antibody	Some pathogens (such as poliovirus) infect cells that cannot be replaced (eg, neurons). Neutralizing antibody is essential to prevent infection of such cells
Induces protective T cells	Some pathogens, particularly intracellular, are more effectively dealt with by cell-mediated responses
Practical considerations	Low cost per dose Biological stability Ease of administration Few side-effects

Figure 14-23 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

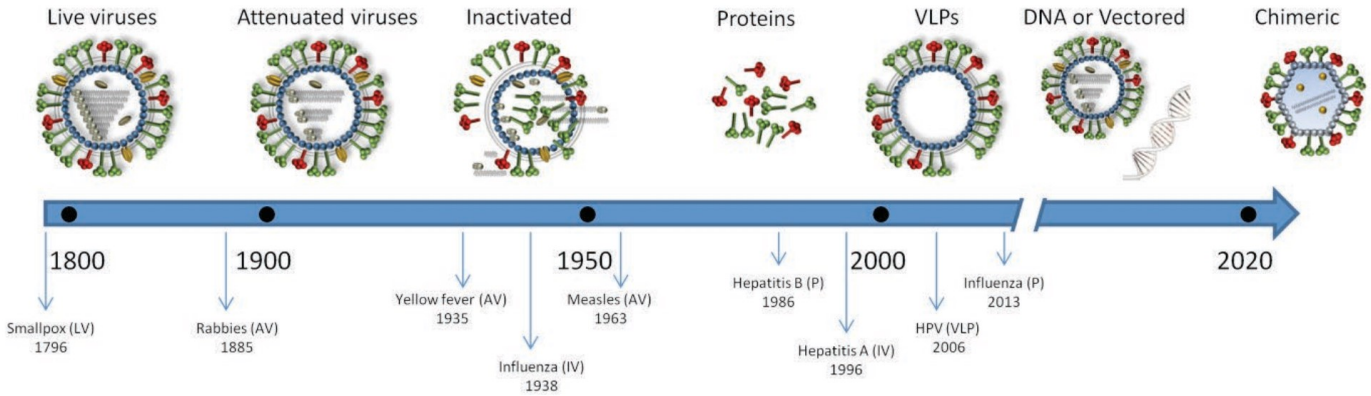
JENIS-JENIS VAKSIN

- Generasi pertama: mengandung mikroorganisme hidup yang dilemahkan
- Generasi kedua: mengandung mikroorganisme yang dimatikan
- Generasi ketiga: dikenal sebagai vaksin rekombinan atau sub-unit, mengandung fragmen antigenik dari mikroorganisme yang dapat merangsang respon imun
- Generasi keempat: Vaksin DNA

Technological
Milestones

Experimental Sciences – 18 -19th century	Tissue Culture – 1930s	Recombinant DNA – 1980s	Synthetic Biology – 2000s ....
Inoculation	Embryonated Eggs Animal Cell Cultures	DNA Sequencing Cloning PCR Gene Delivery	DNA and Peptide Synthesis

Vaccines Types



(Rodrigues ***et al.,*** 2015, Biotechnol. J.)

Peluang Penemuan Obat dan Vaksin Baru

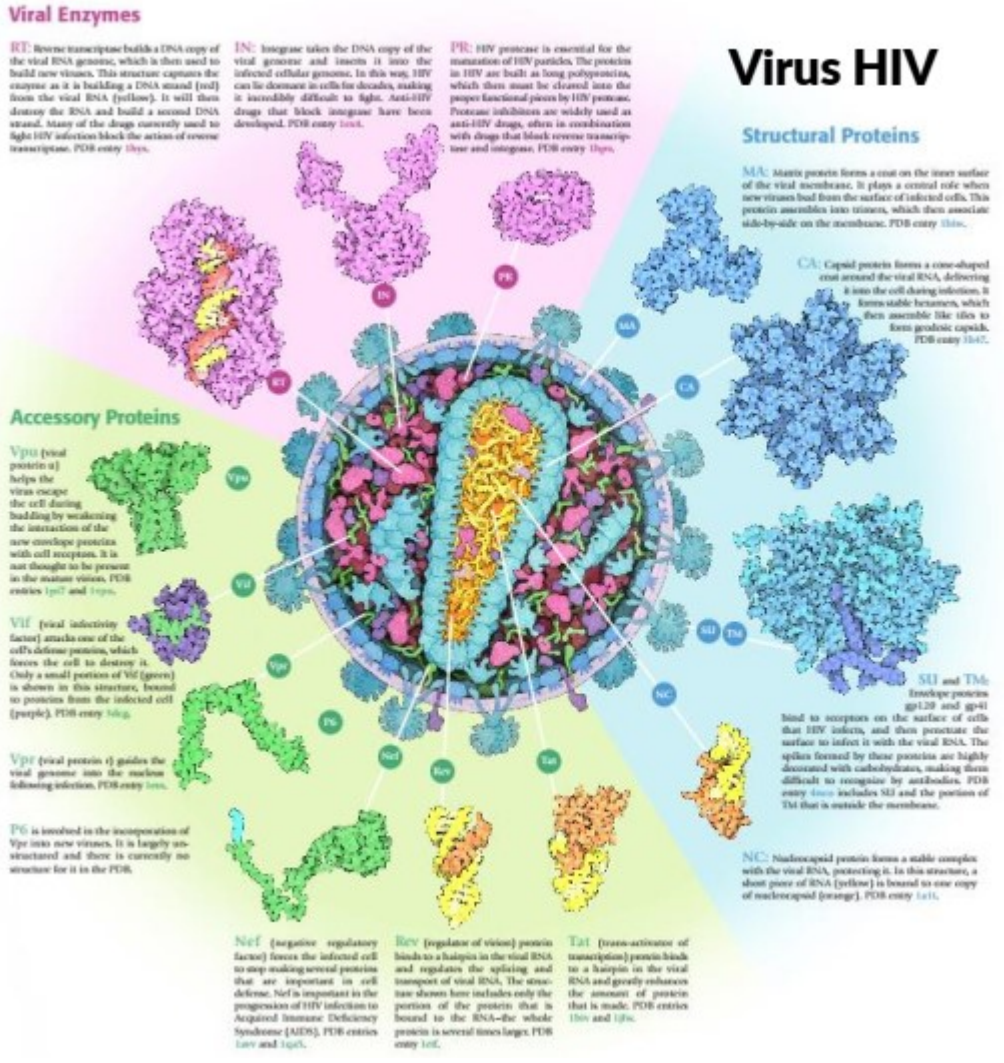
Big Data Gen & Pro

Saat ini kita dapat mengetahui rupa dan sifat virus sampai tingkat atomik

RCSB PDB PROTEIN DATA BANK

157145 Biological Macromolecular Structures Enabling Breakthroughs in Research and Education

Open Access!



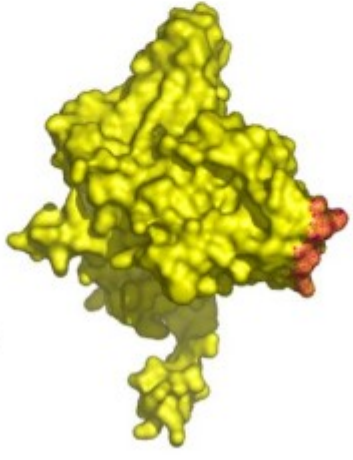
NATURE REVIEWS | MICROBIOLOGY
VOLUME 10 | DECEMBER 2012

Structural vaccinology starts to deliver

Philip R. Dormitzer, Guido Grandi and Rino Rappuoli

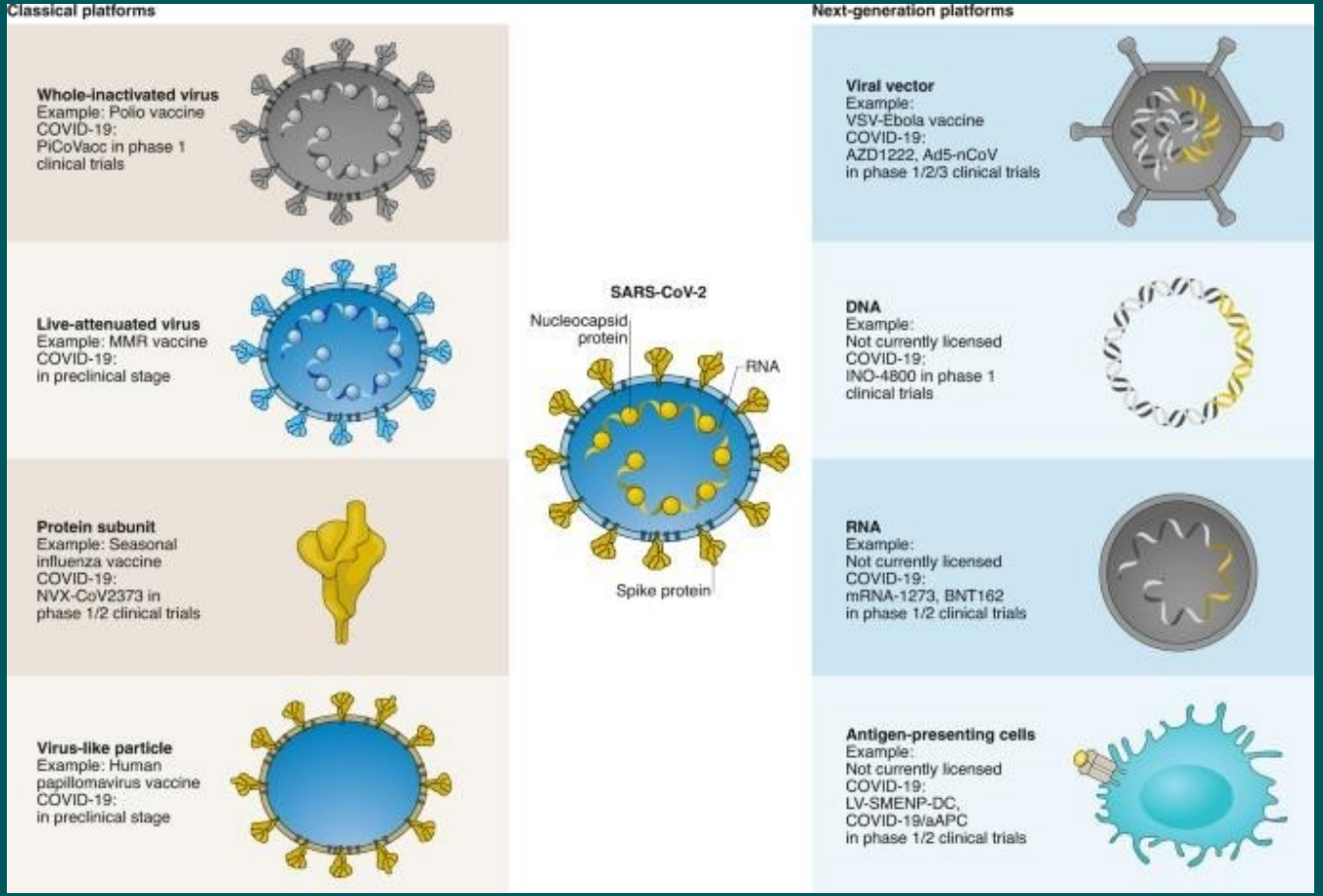
Abstract | Following the impact of the genomics revolution on vaccine research and the development of reverse vaccinology, it was predicted that another new approach, structure-based antigen design, would become a driving force for vaccine innovation. Now, 5 years on, there are several examples of how structure-based design, or structural vaccinology, can deliver new vaccine antigens that were not possible before. Here, we discuss some of these examples and the contribution of structural vaccinology to our understanding of the protective epitopes of important bacterial and viral pathogens.

>PATHOGEN PROTEIN
KVFGRCELAAAMKRHGLDNYR
GYSLGNWVCAAKFESNF



Rational Vaccine Design

Platform Teknologi Pembuatan Vaksin



Source : nature.com

Vaccine platform technologies have implications for duration of effect, scalability and other vaccine parameters; ~32% of vaccine candidates in development are protein subunit based

Vaccine types		Overview	Disadvantages	Share of pipeline	Examples
Virus	Inactivated	Virus rendered uninfectious using chemicals or heat	Requires large amounts of infectious virus to elicit sufficient antibody response	~7%	**Hep A, flu, polio, rabies**
	Weakened	Virus weakened by passing through cells until it picks up mutations that make the virus less able to cause disease	Contains living pathogens and thus cannot be given to immunocompromised individuals	-	**MMR, varicella**
Viral vector	Replicating	Virus replicates within cells to initiate a strong immune response; delivers antigens to select target cells/tissues	Immunity to the vector could lessen efficacy	~9%	**Ebola**
	Nonreplicating	Adenovirus typically used in gene therapy	Requires booster shots and/or high doses to induce long-term immunity	~12%	**No licensed vaccines**
Nucleic acid	DNA	Nucleic acid inserted into human cells that produce copies of the virus protein; electroporation is used for DNA uptake into cells, while mRNA is encased in a lipid coat	Considered safe and easy to develop; however, the efficacy of these vaccines remains unproven	~8%	**No licensed vaccines**
	mRNA			~13%	
Protein-based	Protein subunit	Vaccines that involve injecting virus proteins directly into the body — fragments that mimic the outercoat can also be used	May require adjuvants and multiple doses for efficacy; challenging to manufacture; can trigger a strong immune response	~32%	**Pertussis, Hep B**
	Viruslike particles			~7%	

Source: *Nature*; Publichealth.org; *MedlinePlus*; ScienceDirect; HHS; NCBI; WHO; L.E.K. research and analysis

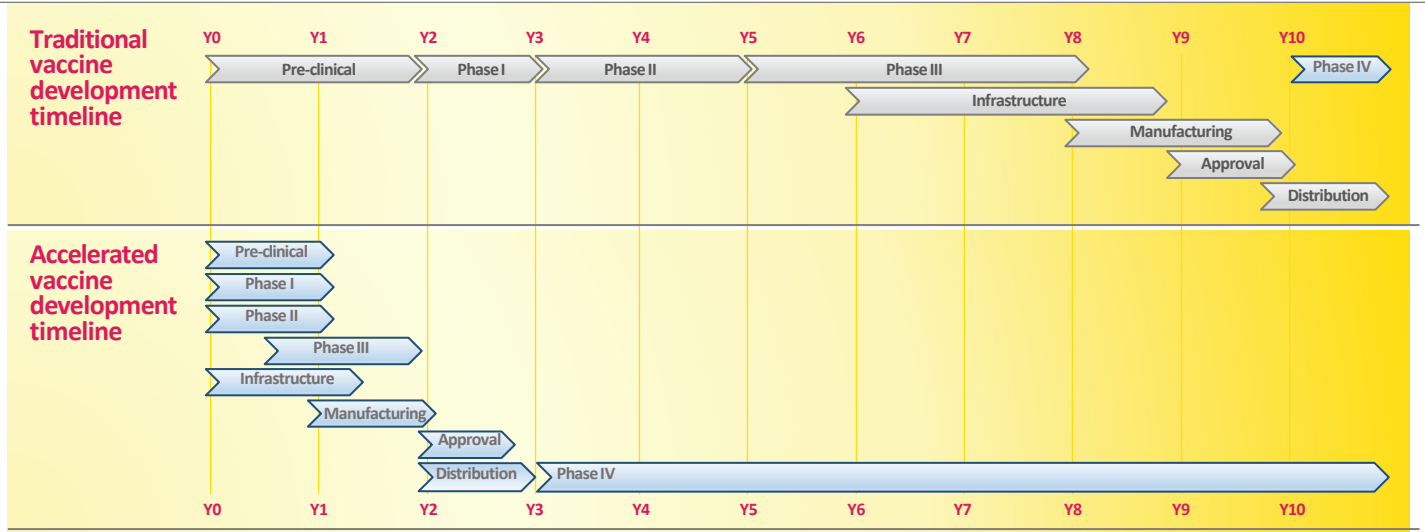
Steps in vaccine development

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

- **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 population
- **Human challenge studies**
  Studies in which a vaccine is given followed by the pathogen against which the vaccine is designed to protect. Such trials are uncommon in people as they present considerable ethical challenges

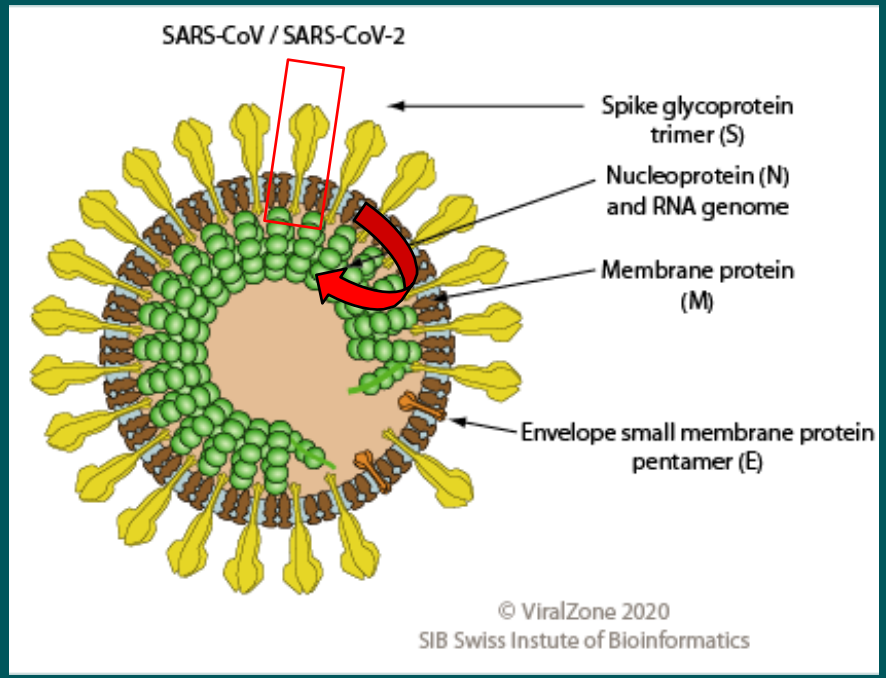
10

COVID-19 vaccine accelerated development



- Normal vaccine development performs each step in sequence
- To accelerate COVID-19 vaccine development, **steps are done in parallel**
- All usual safety and efficacy monitoring mechanisms remain in place; such as adverse event surveillance, safety data monitoring & long-term follow-up
- **Phase IV post-marketing surveillance** for side effects is critical and essential

SARS-Cov-1, MERS dan SARS-Cov-2

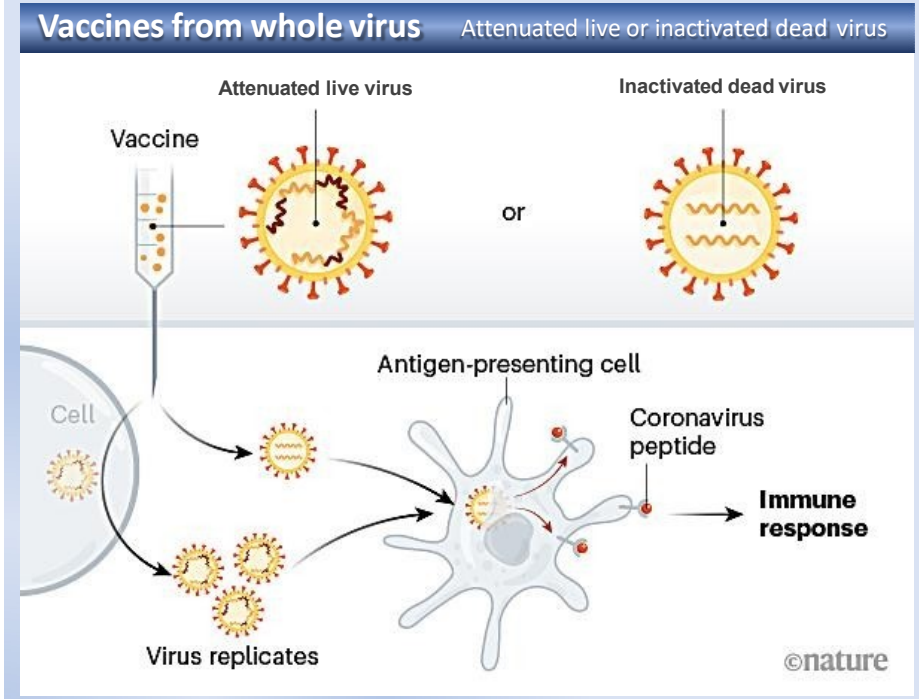


- Single stranded (SS) RNA Positive strand virus
- Keluarga Coronaviridae
- Genus Betacoronavirus
    - SARS-Cov : SARS Epidemic (2002-2003)
    - MERS-Cov : MERS Epidemic (2012)
    - SARS-Cov-2 : COVID-19 Pandemic (2019-sekarang)

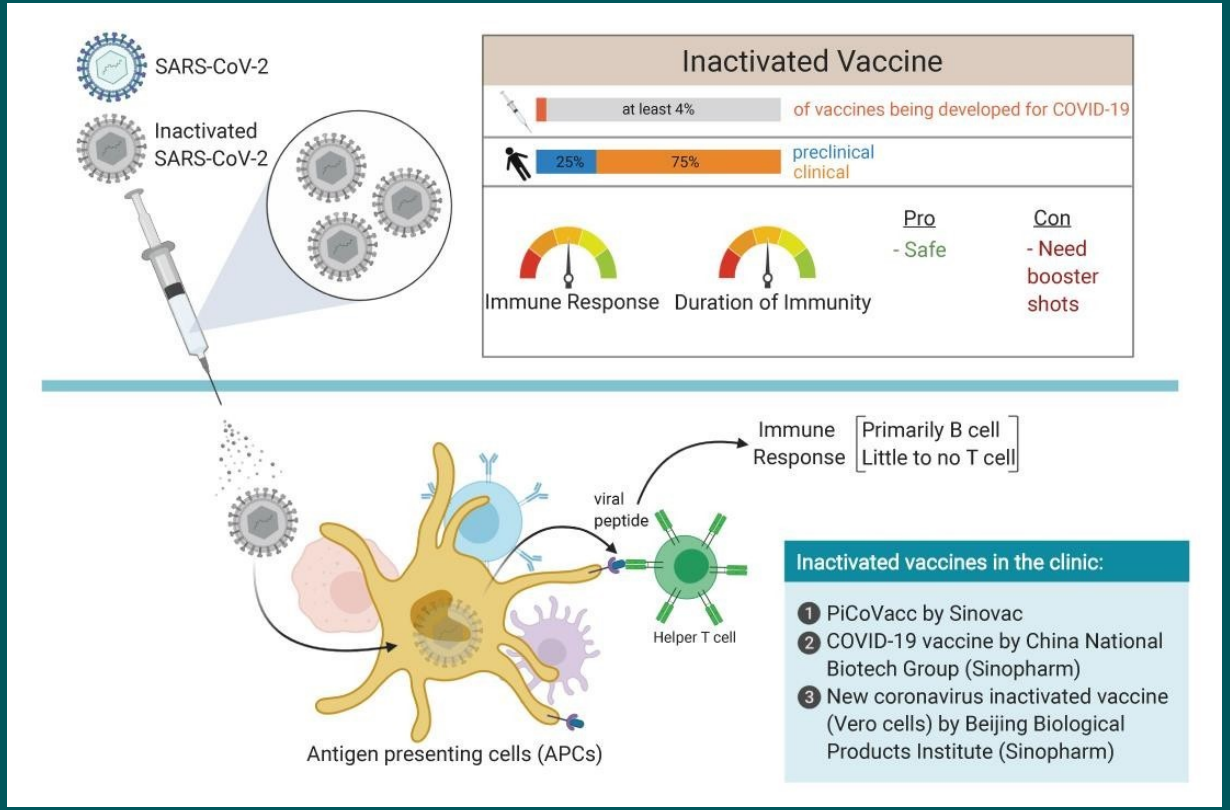
Virus vaccines

- **Virus is selected, modified (weakened) or completely inactivated** so that it will not cause disease

Note:
This illustration shows injectable vaccines. Some vaccines in this category are administered orally

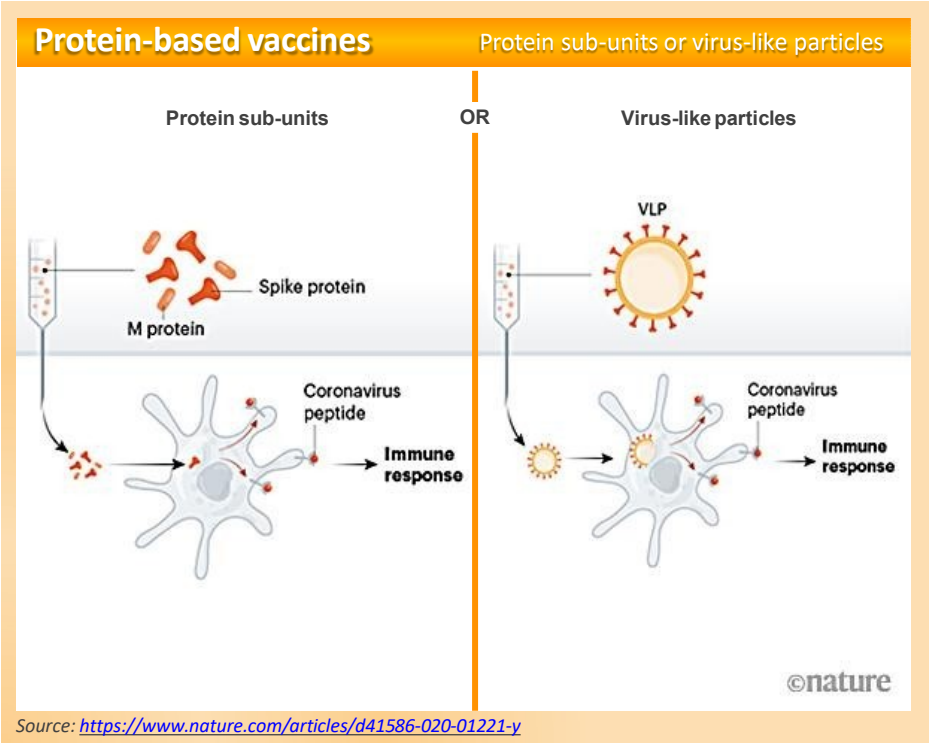


Source: https://www.nature.com/articles/d41586-020-01221-y


SARS-CoV-2
Inactivated SARS-CoV-2
Inactivated Vaccine
at least 4%
of vaccines being developed for COVID-19
25%
75%
preclinical
clinical
Immune Response
Duration of Immunity
Pro
- Safe
Con
- Need booster shots
Immune Response
Primarily B cell
Little to no T cell
viral peptide
Helper T cell
Antigen presenting cells (APCs)
Inactivated vaccines in the clinic:
1 PiCoVacc by Sinovac
2 COVID-19 vaccine by China National Biotech Group (Sinopharm)
3 New coronavirus inactivated vaccine (Vero cells) by Beijing Biological Products Institute (Sinopharm)

Protein-based vaccines

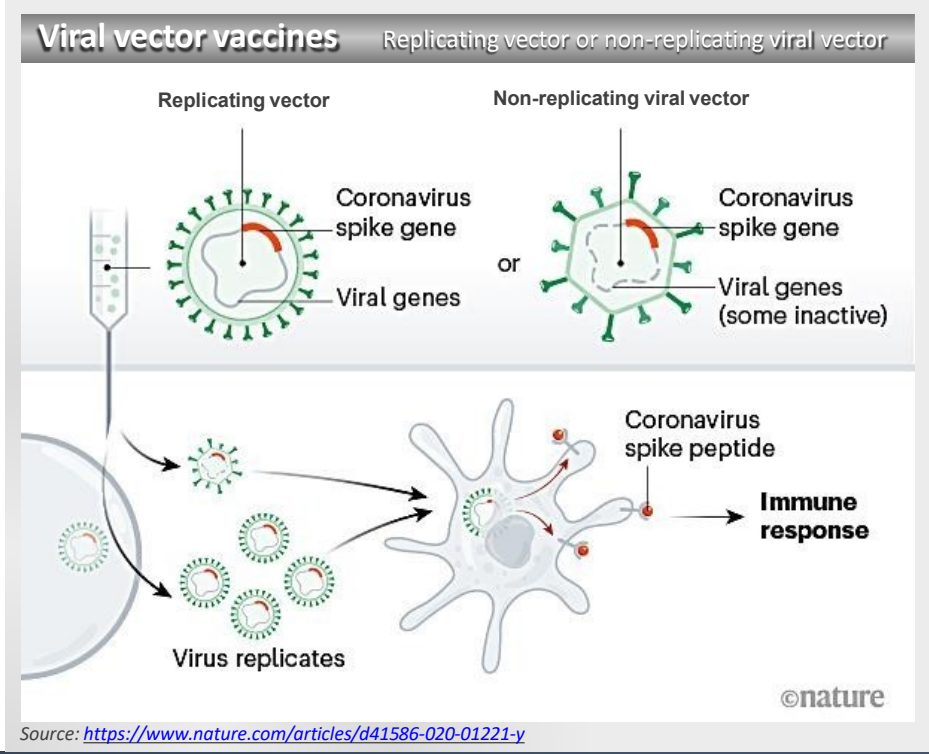
- **A protein is extracted from the virus** (alive or inactivated), purified, and injected as a vaccine
- For coronavirus, this is most commonly the spike protein
- Virus-like particles work in the same way



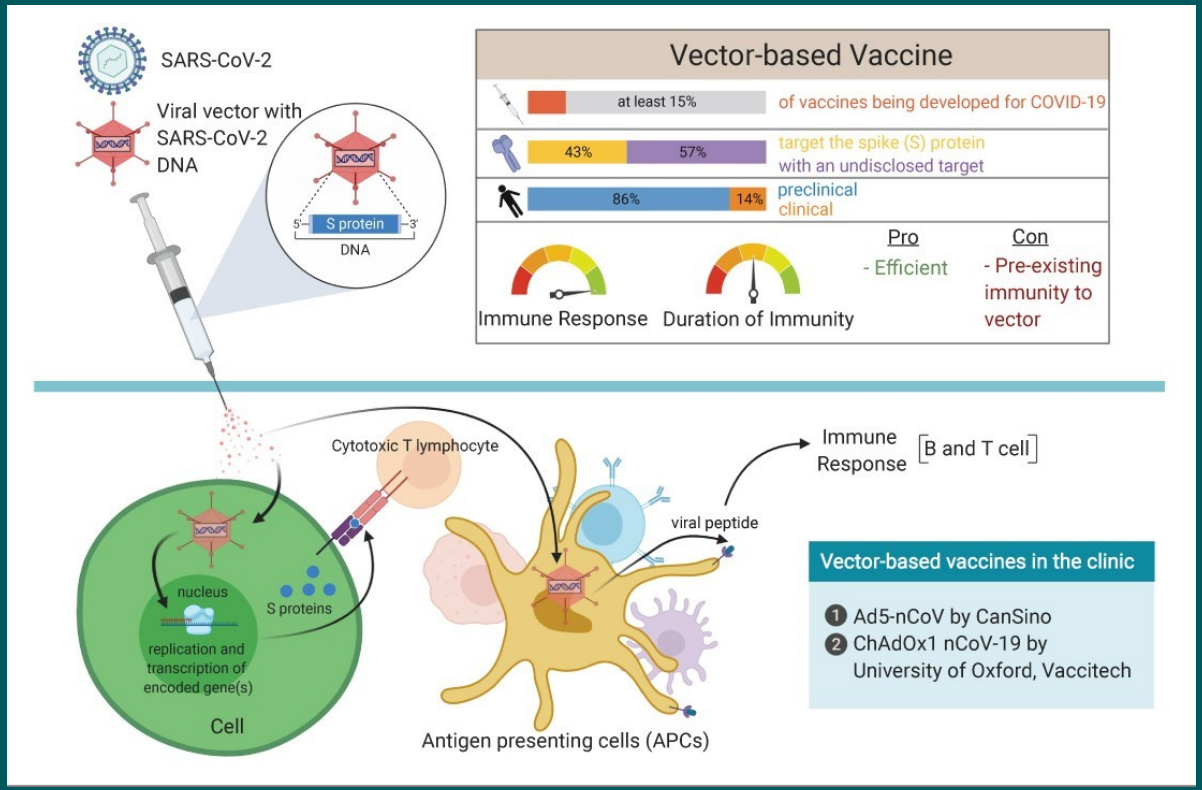
Source: https://www.nature.com/articles/d41586-020-01221-y

Viral vector vaccines

- **The gene for a pathogen protein is inserted into a different virus** that can infect someone without causing disease
- The safe virus serves as a 'platform' or 'vector' to deliver the protein that triggers an immune response
- The safe virus is then injected as a vaccine
- Some replicate (reproduce) in the body and some do not

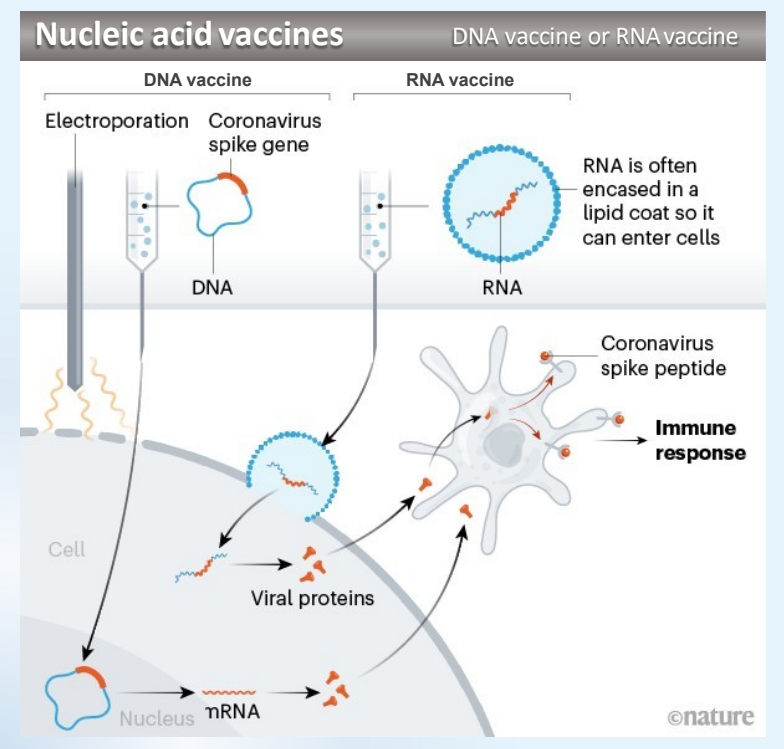


Source: https://www.nature.com/articles/d41586-020-01221-y

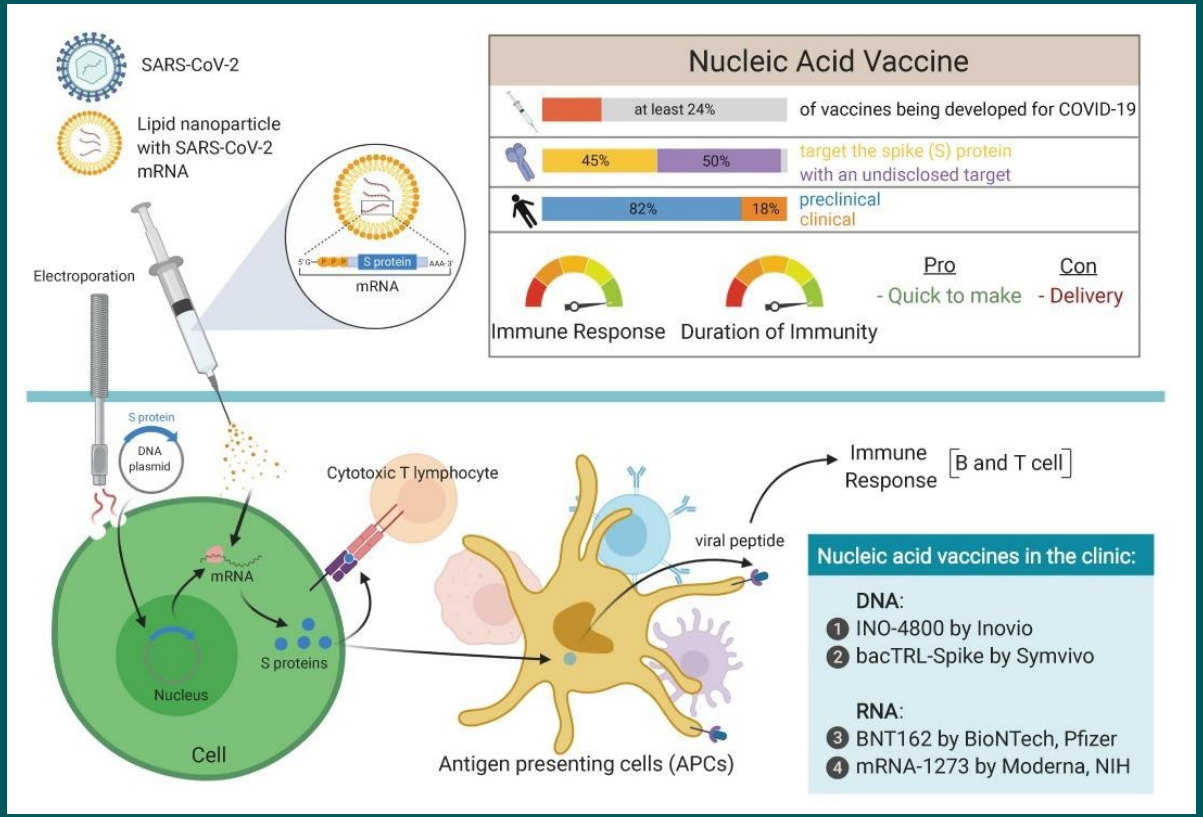

SARS-CoV-2
Viral vector with SARS-CoV-2 DNA
5'
S protein
3'
DNA
Vector-based Vaccine
at least 15%
of vaccines being developed for COVID-19
43%
57%
target the spike (S) protein with an undisclosed target
86%
14%
preclinical
clinical
Pro
- Efficient
Con
- Pre-existing immunity to vector
Immune Response
Duration of Immunity
Cytotoxic T lymphocyte
Immune Response
[B and T cell]
viral peptide
nucleus
S proteins
replication and transcription of encoded gene(s)
Cell
Antigen presenting cells (APCs)
Vector-based vaccines in the clinic
1 Ad5-nCoV by CanSino
2 ChAdOx1 nCoV-19 by University of Oxford, Vaccitech

Nucleic acid vaccines

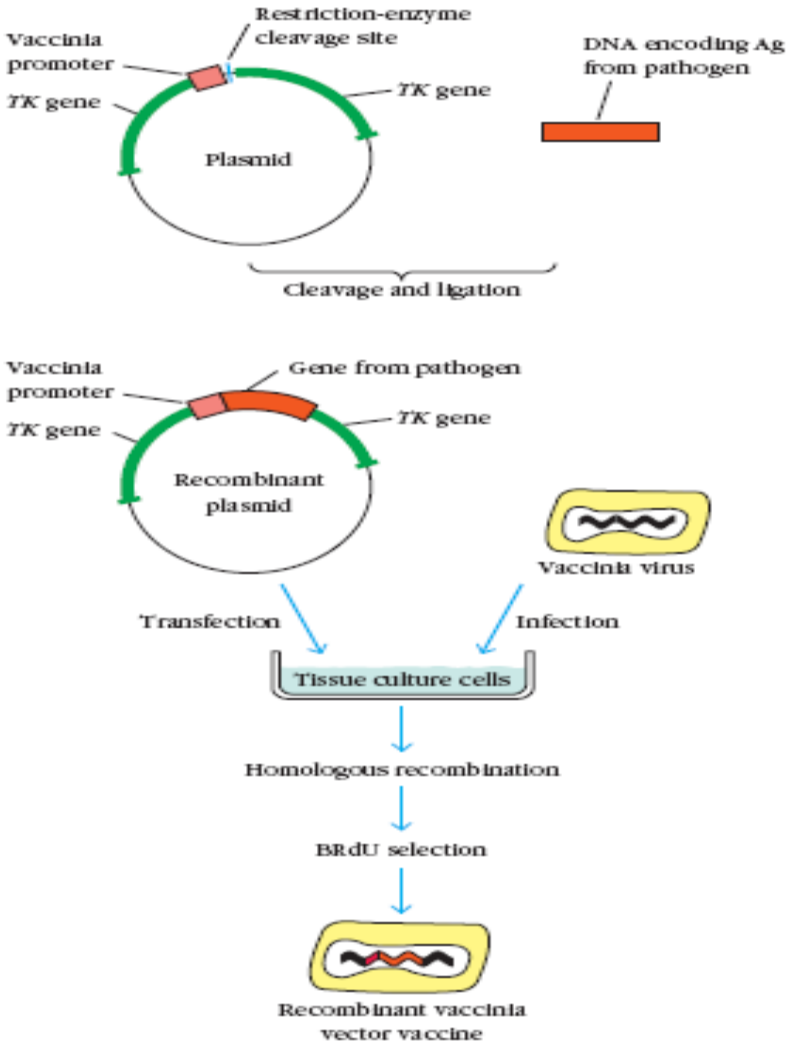
- Instead of a virus, a protein antigen, or a virus expressing the protein, **nucleic acid coding for the antigen is injected**
- DNA plasmid: enters nucleus, translated to mRNA for expression of protein
- Or mRNA can be injected. More direct (no translation required) but less stable than DNA
- This is new technology – no other vaccines for human use have used this



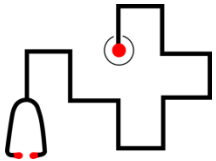
Source: https://www.nature.com/articles/d41586-020-01221-y


SARS-CoV-2
Lipid nanoparticle with SARS-CoV-2 mRNA
Electroporation
S protein
mRNA
Nucleic Acid Vaccine
at least 24%
of vaccines being developed for COVID-19
45%
50%
target the spike (S) protein with an undisclosed target
82%
18%
preclinical
clinical
Pro
- Quick to make
Con
- Delivery
Immune Response
Duration of Immunity
S protein
DNA plasmid
Cytotoxic T lymphocyte
mRNA
S proteins
Nucleus
Cell
viral peptide
Immune Response
[B and T cell]
Antigen presenting cells (APCs)
Nucleic acid vaccines in the clinic:
DNA:
1 INO-4800 by Inovio
2 bacTRL-Spike by Symvivo
RNA:
3 BNT162 by BioNTech, Pfizer
4 mRNA-1273 by Moderna, NIH

VAKSIN
REKOMBINAN



Rekombinan Vs. Tradisional



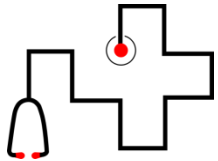
Recombinant

- Hanya menggunakan DNA dari organisme menular.
- Menghindari risiko menggunakan organisme menular yang sebenarnya.
- Menyediakan baik humoral & imunitas sel dimediasi

Traditional

- Menggunakan bentuk lemah atau dibunuh organisme menular.
- Buat kemungkinan resiko vaksin menjadi fatal.
- Memberikan kekebalan terutama humoral

Vaksin Sistemik Vs Vaksin Lokal



- vaksin sistemik

intramuskular/subkutan/iv

respons imun sistemik (IgG)

- vaksin lokal:

oral/intranasal/topikal

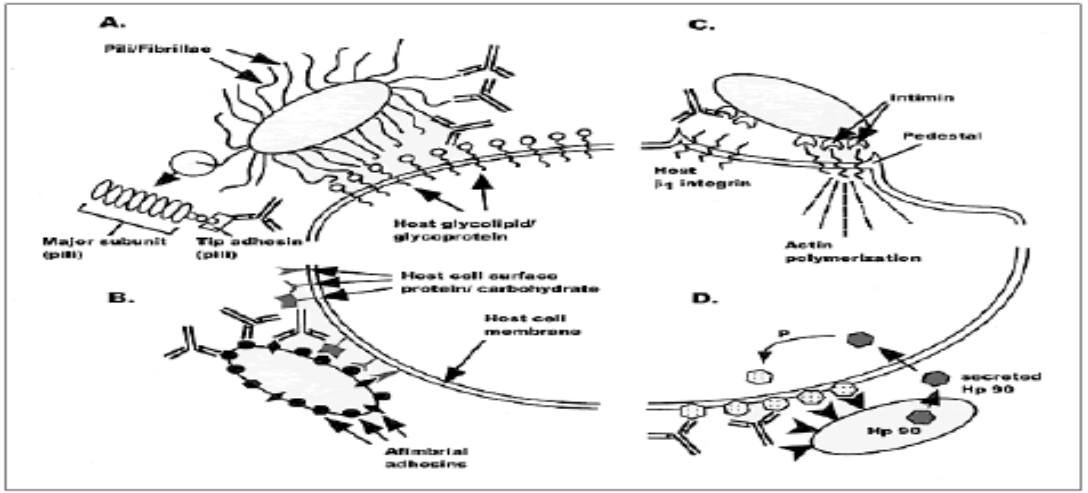
respons imun lokal/mukosa (sIgA)

VAKSIN LOKAL

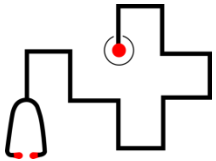
- Bekerja pada tahap pertama infeksi:

Adhesi/invasi

Sebelum patogen mas uk ke daerah yg lebih dalam



ADJUVANT



- Protein/komponen patogen/patogen mati yang tidak atau kurang imunogenik

– Respons adaptif yang kuat

– Senyawa yang meningkatkan imunogenitas bila dicampur antigen (pada proses awal)

- Karier yang membentuk ikatan kovalen (pada seluruh pro ses)

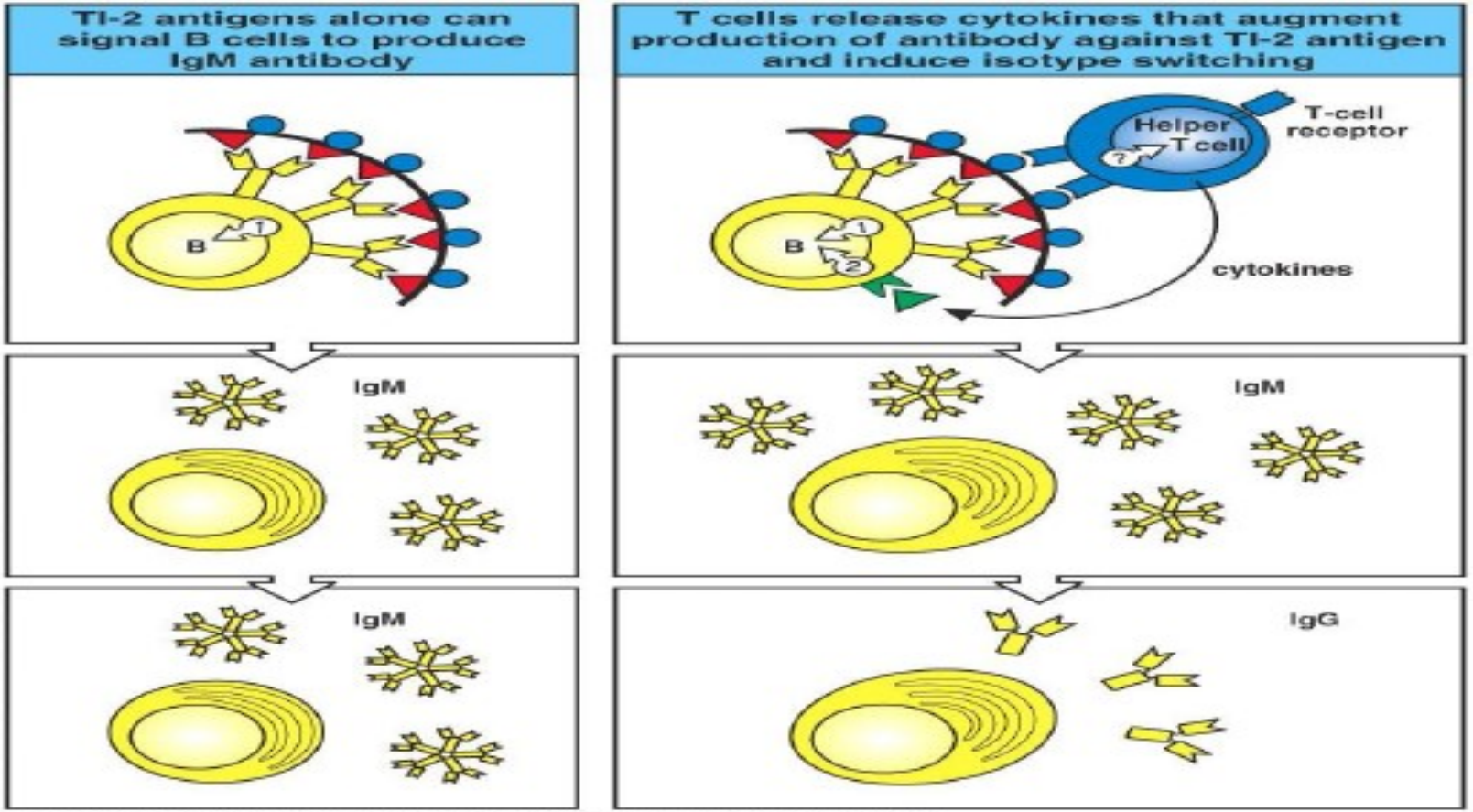


Figure 9-17 Immunobiology, 6/e. (© Garland Science 2005)

Adjuvants that enhance immune responses

Adjuvant name	Composition	Mechanism of action
Incomplete Freund's adjuvant	Oil-in-water emulsion	Delayed release of antigen; enhanced uptake by macrophages
Complete Freunds adjuvant	Oil-in-water emulsion with dead mycobacteria	Delayed release of antigen; enhanced uptake by macrophages; induction of co-stimulators in macrophages
Freunds adjuvant with MDP	Oil-in-water emulsion with muramyldipeptide (MDP), a constituent of mycobacteria	Similar to complete Freund's adjuvant
Alum (aluminum hydroxide)	Aluminum hydroxide gel	Delayed release of antigen; enhanced macrophage uptake
Alum plus *Bordetella pertussis*	Aluminum hydroxide gel with killed *B. pertussis*	Delayed release of antigen; enhanced uptake by macrophages; induction of co-stimulators
Immune stimulatory complexes (ISCOMs)	Matrix of Quil A containing viral proteins	Delivers antigen to cytosol; allows induction of cytotoxic T cells

Figure A-4 Immunobiology, 6/e. (© Garland Science 2005)

What knowledge is needed to produce a vaccine ?

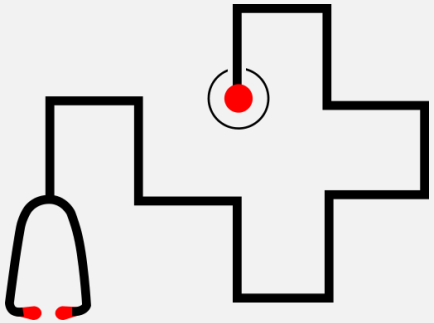
1. Understand life–cycle of pathogen

   → find best target stage.

2. Understand immune mechanisms stimulated by parasite → humoral /cellu lar response ?

3. Understanding the incubation period of the pathogen.

- A short incubation period (e.g. influenza) results in symptoms before me mory cells are activated. Circulating antibodies are important in these ins tances.
- Longer incubation periods (e.g. polio) allow memory cells to become acti vated prior to onset of symptoms



Thank you