What do we know about coronavirus vaccines?

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Coronavirus family

The Coronavirus family Coronaviridae is composed of 3 subfamilies: Coronavirinae, Orthocoronavirinae and unclassified Coronaviridae. Ortocoronavirinae includes common alpha-, beta-, gamma- and deltacoronavirus. Two types of alpha coronaviruses (229E and NL63) and two types of beta coronaviruses (OC43 and HKU1) circulate in humans and cause colds. More pathogenic human coronaviruses pose a serious threat to health. They cause Severe Acute Respiratory Syndrome (SARS) from 2002, Middle Eastern Respiratory Syndrome (MERS) from 2012, and COVID-19 from the end of 2019. Causative agents are beta-coronaviruses: SARS coronavirus (SARS-CoV), MERS coronavirus (MERS-CoV) and 2019-nCoV, now officially called SARS-CoV-2. Within 7 months, it infected more than 9,000,000 people, as of 06/23/2020, it caused more than 479,778 deaths worldwide. In some cases, the course of the disease is mild, in others it can develop into pneumonia, which can be fatal. Most patients recover; but people with a weakened immune system die, in particular the elderly. Vaccines significantly reduce the risk of infection, stimulating the body's natural defense mechanisms and developing immunity to diseases.

- **Coronaviridae**
  - **Coronavirinae**
    - **unclassified Coronavirinae**
  - **Orthocoronavirinae**
    - **Alphacoronavirus**
    - **Betacoronavirus**
    - **Deltacoronavirus**
    - **Gammacoronavirus**
    - **unclassified Orthocoronavirinae**
  - **unclassified Coronaviridae**
    - **Guangdong chinese water skink coronavirus**
    - **Gull coronavirus**
    - **Rhinolophus pusillus coronavirus**
    - **Coronaviridae sp.**

Novel coronavirus (a new coronavirus that has not been previously identified). Synonims:
2019-nCoV
COVID-19
COVID-19 virus
SARS2
Wuhan coronavirus
Wuhan seafood market pneumonia virus
Human coronavirus 2019
COVID19
HCoV-19
SARS-2
SARS-CoV2

Taxonomy

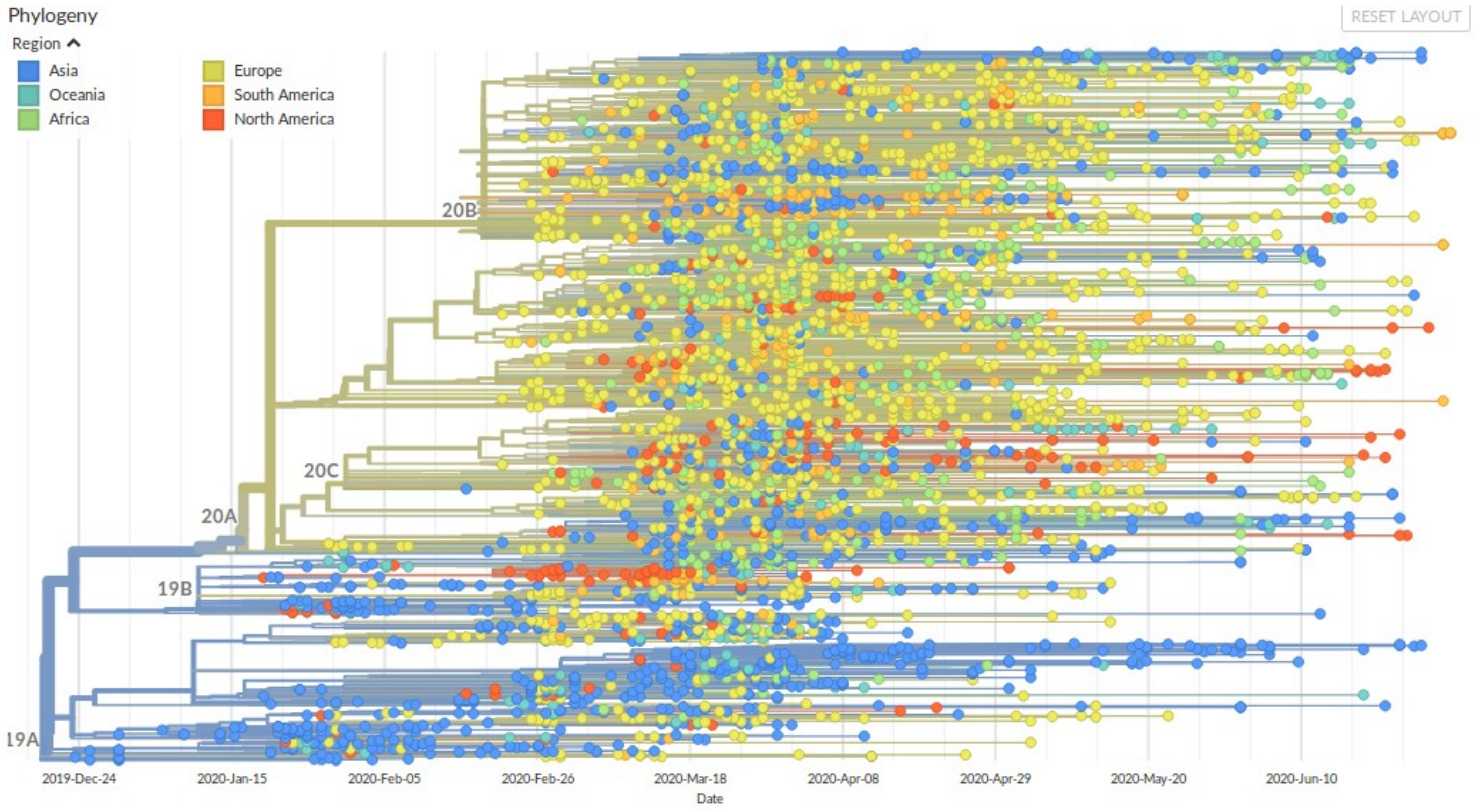
Viruses →Riboviria →Orthornavirae →Pisuviricota →Pisoniviricetes →Nidovirales →Cornidovirineae→Coronaviridae → Orthocoronavirinae →Betacoronavirus →Sarbecovirus →Severe acute respiratory syndrome-related coronavirus → **Severe acute respiratory syndrome coronavirus 2**

Phylogeny

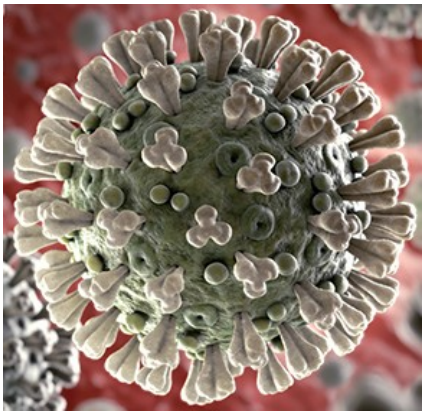
More closely related to bat-SL-CoVZC45 and bat-SL-CoVZXC21 than SARS

Genome of virus SARS-CoV-2

As the pathogen multiplies and spreads, its genome passes through many replications and accumulates mutations. There are 3437 genomes sampled between Dec 2019 and Jul 2020 www.nextstrain.org/ncov/global The COVID-19 virus does not mutate very fast. It does so 10 times more slowly than the influenza virus. Its genome consists of about 30,000 nucleotides. Most mutations accumulate in the receptor-binding region. Thousands of complete genomes are now available, and this number is increasing by hundreds every day. Genomic epidemiology of novel coronavirus - global subsampling presented on nexstrain website with ability of filtering by submission date, location, country, originating lab...



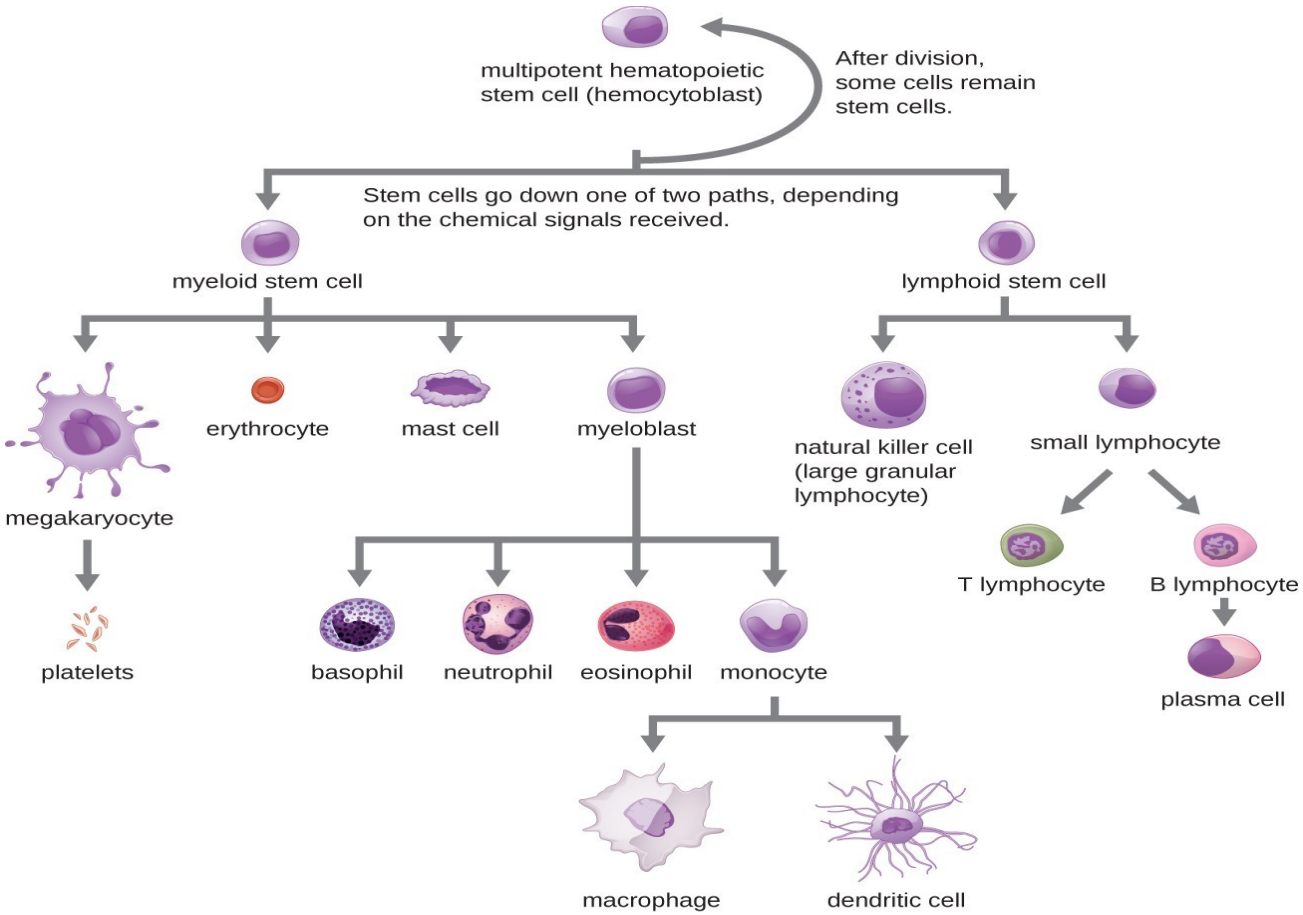
The ways the virus enters the cells



SARS-CoV-2 are spherical and have spikes protruding from their surface, giving them a crown-like appearance under the electron microscope. The virus can entry via two pathways: plasma membrane or endosome. Coronavirus membrane fusion occurs after spike protein's S1 region binds to angiotensin converting enzyme 2 (ACE2) of the surface of many types of human cells. This is the first step in the viral penetretion process. ACE2 is attached to the cell membrane of club cells of distal bronchioles and type 2 pneumocytes in alveolar epithelium. Club cells secrete a substance that protect against airway inflammation and oxidative stress. Type 2 pneumocytes synthesize surfactant. ACE2 is also found in the cerebral cortex, arterial and venous endothelial cells, heart, kidneys, liver, enterocytes… When the SARS-CoV-2 binds to ACE2, it prevents ACE2 from performing its normal function (cutting up angiotensinogen). Ang II accumulates, it increase the inflammation in the tissues, oxidative stress and fibrosis.
Which pathway is used depends on presence of proteases. S proteins may be cleaved by human cells` proteases, including furin, trypsin, elastase, transmembrane serine proteinases TMPRSS-2, TMPRSS-4. If these proteases present on surface of human cell near a spike–ACE2 pair they cleave the spike protein of virus to expose the fusion peptide region of virus and it inserts into the human cell membrane.

If proteases are not present near a spike–ACE2 pair the virus enters the cell by endocytosis. Proteases present in the endosome, including one called cathepsin L, can cleave the spike protein and expose its fusion peptide region. It fuses the viral membrane with the membrane of the endosome and thereby induces the penetration of viral RNA into the cell. Nafomastat, MI-1851 and PIKfyve inhibitors block proteases involved in spike protein cleavage.

Immunity



When viruses enter cells, they multiply. The immune system recognizes them as something extraneous to the body and the immune cells try to fight them with the help of macrophages, B- and T-lymphocytes. The foreign substances causing this reaction are called antigens and are usually proteins or polysaccharides.

Macrophages and dendritic cells (DC) are members of the mononuclear phagocyte system; they swallow up and digest viruses and dying cells. Their activation cause excessive pro-inflammatory cytokine responses or cytokine storm resulted in illness severity. Then they move to the nearest lymph nodes and introduce the antigenlymphocytess to other immune cells to induce a strong specific response through the production of antigen-specific antibodies that bind a part of an antigen, or epitope.

T cells, like all other white blood cells involved in innate and adaptive immunity, are formed from **hematopoietic stem cells** in the bone marrow after which immature T lymphocytes enter the bloodstream and travel to the thymus for maturation (**thymocytes)**. Three steps of thymic selection eliminate 98% of thymocytes. The remaining 2% exit the thymus, migrate through the bloodstream and lymphatic system to sites of secondary lymphoid organs, such as the lymph nodes, spleen, and tonsils, where they await activation through the presentation of specific antigens by **antigen-presenting cells (APCs)**. Until they are activated, they are known as **mature naïve T cells**.

T cells can be categorized into three distinct classes: **helper T cells**, **regulatory T cells**, and **cytotoxic T cells**. These classes are differentiated based on their expression of certain surface molecules, their mode of activation, and their functional roles in adaptive immunity. All T cells produce **cluster of differentiation (CD) molecules**, cell surface glycoproteins that can be used to identify and distinguish between the various types of white blood cells. Although T cells can produce a variety of CD molecules, **CD4** and **CD8** are the two most important used for differentiation of the classes. Helper T cells and regulatory T cells are characterized by the expression of CD4 on their surface, whereas cytotoxic T cells are characterized by the expression of CD8.

Classes of T cells can also be distinguished by the specific **major histocompatibility complex (MHC)**. Helper T cells and regulatory T cells can only be activated by APCs presenting antigens associated with **MHC II**. In contrast, cytotoxic T cells recognize antigens presented in association with **MHC I.**

The first line of defense is tissue-resident memory T cells (Trm), that comprise $CD4^+$ and $CD8^+$ populations. CD4+ T cells promote the proliferation of neutralizing antibodies, while CD8+ T cells are responsible for the destruction of virally infected cells.

Class	Surface CD Molecules	Activation	Functions
Helper T cells	CD4	APCs presenting antigens associated with MHC II	Orchestrate humoral and cellular immunity
			Involved in the activation of macrophages and NK cells
Regulatory T cells	CD4	APCs presenting antigens associated with MHC II	Involved in peripheral tolerance and prevention of autoimmune responses
Cytotoxic T cells	CD8	APCs or infected nucleated cells presenting antigens associated with MHC I	Destroy cells infected with intracellular pathogens

https://courses.lumenlearning.com/microbiology/chapter/t-lymphocytes-and-cellular-immunity/

Subsets of T lymphocytes:

- T helper cells (Th)
- cytotoxic T cells (Tc) and among them NKT – natural killer T cells
- regulatory T cells (Treg)
- exhausted/tired, anergic T lymphocytes
- naïve T cells
- memory T lymphocytes:
  - effector memory T cells (Tem)
  - central memory T cells (Tec)
  - Peripheral Memory (Tpm)
  - Tissue Resident Memory (Trm)
- CD4-Positive T lymphocytes (CD4+)
- CD8-Positive T lymphocytes (CD8+)

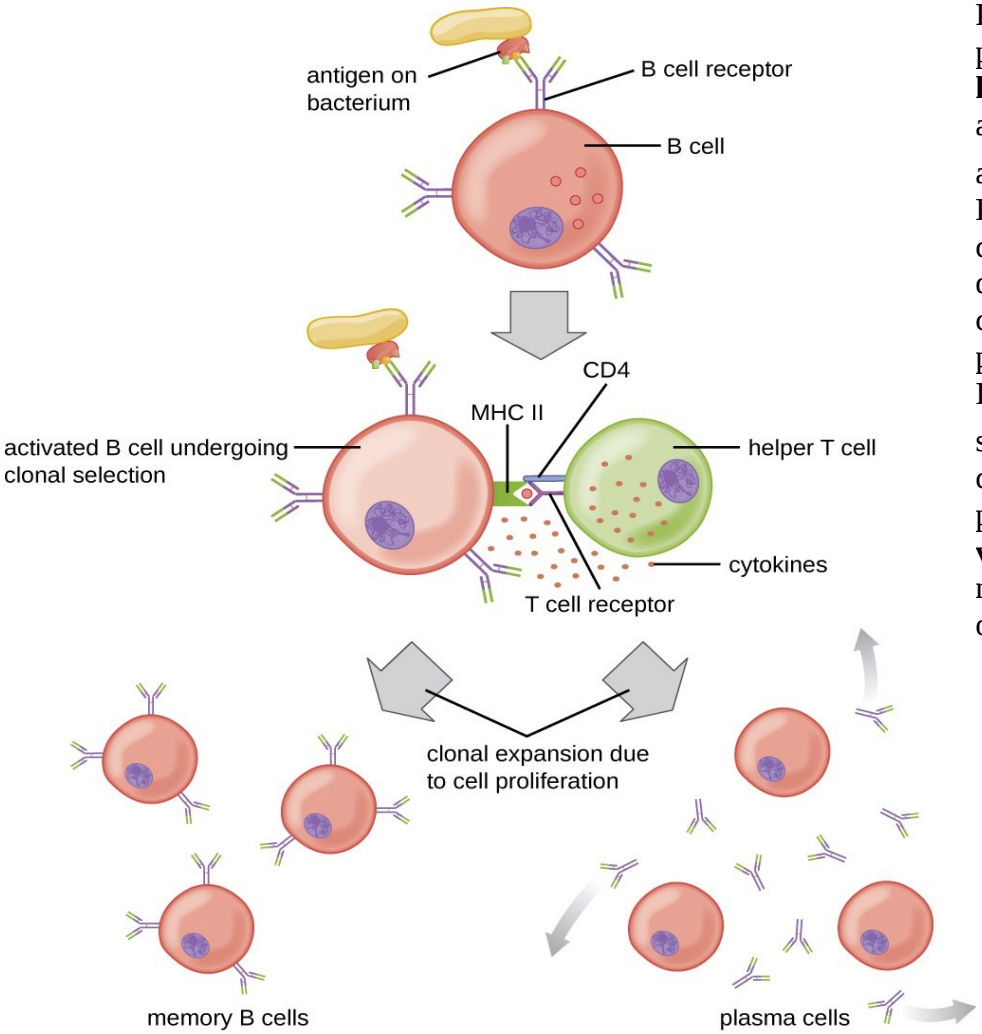
The **T-cell receptor (TCR)** has two peptide chains: **constant region** and the **variable region,** provides the antigen-binding site. Possible combinations of TCR gene segments produce millions of unique TCRs. The epitope is presented within the MHC II of **APCs.** The helper T-cell must recognize both a foreign epitope and its own "self" APC antigen. For this, involved TCR and CD4 on Th. Activated Th proliferates, produce clonal naïve Th:

Subtype	**Functions**
T_H1 cells	Stimulate cytotoxic T cells and produce memory cytotoxic T cells
	Stimulate macrophages and neutrophils for effective intracellular killing of pathogens
	Stimulate NK cells to kill more effectively
T_H2 cells	Stimulate B cell activation and differentiation into plasma cells and memory B cells
	Direct antibody class switching in B cells
T_H17 cells	Stimulate immunity to specific infections such as chronic mucocutaneous infections
Memory helper T cells	"Remember" a pathogen and mount a strong, rapid secondary response upon re-exposure

Certain bacteria and viruses with superantigen can trigger unregulated response, **MHC II** molecules present superantigen and TCR, CD4 bind it without specific foreign epitope recognition. The result is an excessive, uncontrolled release of cytokines, often called a **cytokine storm** with excessive inflammatory response.

Lymphoblasts destined to become B cells do not leave the **bone marrow**. Immature B cells that pass the selection in the bone marrow then travel to the **spleen** for their final stages of maturation. There they become **naïve mature B cells** with 100,000 **B-cell receptors (BCRs)** on its membrane, **IgD** and **IgM.** They have four peptide chains: two identical heavy chains and two light chains connected by into a basic "Y" shape that has two **antigen-binding sites.** Hundreds of gene segments provide millions of unique antigen-binding sites for the BCR. While TCRs only recognize protein epitopes, BCRs can recognize epitopes associated with different molecular classes (e.g., proteins, polysaccharides, lipopolysaccharides).

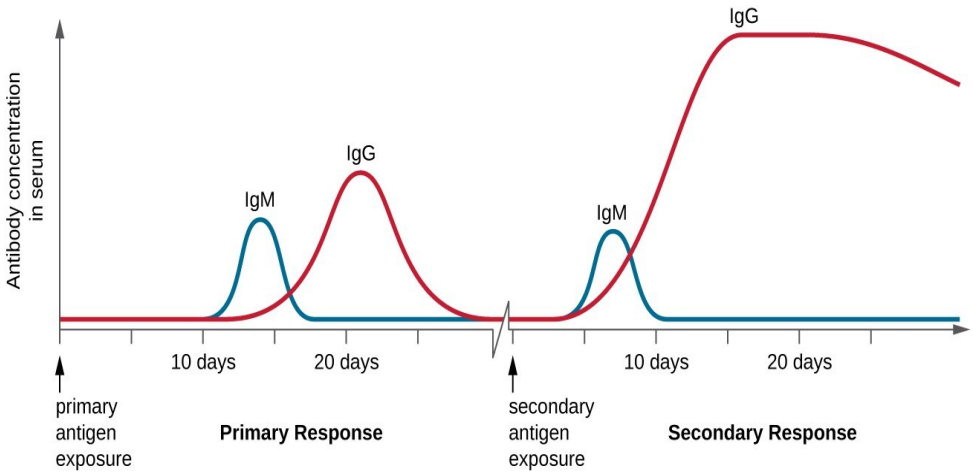
Activation of a B cell by a protein antigen requires presenting it with MHC II to helper T cells. Protein antigens are classified as **T-dependent antigens**. In contrast, polysaccharides, lipopolysaccharides, and other nonprotein antigens are considered **T-independent antigens**. Once a B cell is activated, it undergoes **clonal proliferation** and daughter cells differentiate into plasma cells, that secrete large quantities of antibodies. The surface BCRs disappear and the plasma cell secretes **pentameric IgM** molecules that have the same antigen specificity as the BCRs. The T cell-independent response is short-lived and does not result in the production of **memory B cells**.



Protein antigen is processed and presented with **MHC II** recognized by **helper T cells** specific to the same antigen. Activated **T_H2 cells** produce and secrete **cytokines** that activate the B cell and cause proliferation into clonal daughter cells, stimulate the differentiation of activated B cell clones into **memory B cells** and plasma cells. After initial secretion of IgM, **cytokines** secreted by T_H2 cells stimulate **class switching** of plasma cells from IgM production to production of **IgG**, **IgA**, or **IgE** The **variable region** is not changed, so the new class of antibody retains the original epitope specificity.

https://courses.lumenlearning.com/microbiology/chapter/b-lymphocytes-and-humoral-immunity/

With the first exposure to a protein antigen, a T cell-dependent **primary antibody response** occurs. The initial stage of the primary response is a **lag period**, or **latent period**, of approximately 10 days, during which no antibody can be detected in serum. The secondary immune response occurs when the second time (3rd, 4th, etc.) the person is exposed to the same antigen. At this point immunological memory has been established and the immune system can start making antibodies immediately. S**econdary response** occurs more quickly and forcefully than the primary response. The production of IgG is significantly higher. They make 100-1000 times more antibodies than they did the first time.



An important property of **memory B cells** is their ability to have a very long life, what is decisive for vaccination. It is known that the level of antigen-specific memory B cells remains relatively stable for more than 50 years after some types of vaccination. However, there is not enough information about the life span of individual **memory B cells** cells.

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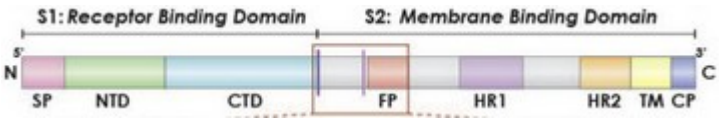
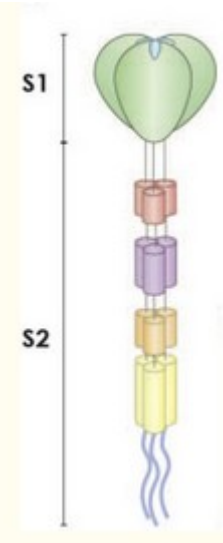
Types of Antigens

SARS-CoV-2 are enveloped, single-stranded RNA viruses encodes for a 27 proteins divided into structural and non-structural proteins. The fundamental are four major structural proteins: spike (S), envelope (E), membrane (M) and nucleocapsid (N).



Spike-glycoprotein S plays an important role in the attachment, fusion, penetration, and transmission of the virus. Spike includes S1 and S2 subunits. S1 has N- and C- terminal portions. Either N-terminal domain (NTD) or C-terminal domain (CTD) can serve as the receptor-binding domain (RBD), that binding the virion to the ACE2. The subunit S2 of the virus has fusion peptide (FP), hydrophobic α-helix structure: heptad repeat 1 and 2 (HR1 and HR2), which are contributing to the fusion of membranes. Following is the transmembrane (TM) domain and cytoplasmic tail.



The spike is cleaved by proteases at the S1 / S2 border or within the S2 subunit, while the external part is removed and the internal fusion peptide (FP) is released. SARS-CoV-2 enters ACE2 cells mainly through endocytosis. Phosphoinositides (acidic phospholipids in cell membranes) are important in endocytosis, they interact with proteins, and inhibition of PIKfyve by apilimod significantly reduced virus entry. Ingibition of endolysosomal cation channel - two pore calcium channel (TPC2) with tetrandrine also decreased virus entry.

Whole Cell Antigens and following antigenes:

(S Protein) *~ Spike Protein* *~ The Full-Length* *~ RBD* *~ NTD* *~ S1 Subunit* *~ FP*	*~ Nucleocapsid (N Protein)*	*~ Membrane (M Protein)*	*~ Envelope (E Protein)*	*~ Hemagglutinin-esterease dimer (HE)*

Protein S on the surface of the virus is an ideal target for a vaccine, spike-directed antibodies can interfere with this binding, thus neutralizing the virus. However, since the genomes of coronaviruses vary greatly, it is better to use antibodies that target different epitopes to avoid the immune escape.

N-protein performs many functions, including nucleocapsid formation, RNA replication, and mRNA transcription. This protein is very antigenic; antibodies to this antigen are detected in 90% of SARS patients. There is debate about whether this protein can be used to develop a vaccine. In any case, there is no doubt that it can be used as a marker in diagnostic tests because of its high immunogenicity.

M protein is able to elicit efficient neutralizing antibodies, contains a T cell epitope cluster that is able to induce a strong cellular immune response and may be used as an antigen for developing the COVID-19 vaccine.

Protein E is not suitable for use as an immunogen, it has channel activity and is an important factor in the virulence and secretion of inflammatory interleukins

HE protein binds sialic acids on the surface of glycoproteins, enhances cell entry and virus spread through the mucosa.

Antibodies

Antibodies are proteins of Immunoglobulins A, G, M, E, D. The most common antibody that protects against viral infections is IgG. Antibodies are found in the blood and tissue fluids, including the linings of the respiratory tract, mucus secretions of digestive system, as well as in tears, saliva, and breast milk. Each B cell creates antibodies against only one specific antigen. Several days pass from the time of the first exposure to antigen until the adaptive response becomes active.

To this day there are 17 antibodies against SARS-COV2 in the registry https://antibodyregistry.org/search?q=SARS-CoV-2 (4 of them have a human host).

- SARS-CoV-2 Spike Antibody
  Antigen: Spike protein S1 Subunit of Receptor Binding Domain sars-cov-2
  Vendor: Active Motif
- SARS-CoV-2 (2019-nCoV) Spike S2 Antibody, Chimeric Mab.
  Antigen:Spike sars-cov-2
  Vendor: Sino Biological (or CanSino Biologics) bind the Nucleoprotein and Spike Protein antigens and are currently undergoing clinical trials. https://clinicaltrials.gov/ct2/show/NCT04313127.

ProSci Inc has engineered different polyclonal, monoclonal, and recombinant antibodies of COVID-19 for research use only and new products are appearing in this list https://www.prosci-inc.com/covid-19/.
Company has Nucleocapsid Monoclonal Antibody. Spike RBD Monoclonal Antibody. Spike-ECD Antibody, etc.

The SARS-CoV-2 and SARS-CoV have about 80% genomic sequence identity. Since high identity, some neutralizing monoclonal antibodies isolated against SARS-CoV, like CR3022, can cross-protect against COVID19, they cross-react to the RBD of SARS-CoV-2 and have cross-neutralizing activity, reducing the penetration of virus.

Serum from recovered patients has been used to treat COVID-19, but sometimes it causes harmful immune responses.

Types of Vaccines

Vaccines help gain immunity by mimicking an infection and causing the immune system to produce T and B lymphocytes and antibodies to remember how to deal with this disease in the future. Vaccination increases the level of circulating antibodies against a specific antigen. As a rule, the body needs several weeks to develop specific immunity after vaccination. Sometimes the vaccine causes minor symptoms that are normal and expected. The first COVID-19 vaccine was developed within 42 days after the Chinese decryption of the genetic code of Sars-CoV-2, but the creation of new vaccines remains difficult, a time-consuming process includes the mandatory phases of clinical trials. For example, a SARS vaccine has been under engineering since 2003, but the development is not yet complete, although at the present time it can be very useful. It has been found that immune cross-reactivity with SARS-CoV is very limited. Different technologies are being evaluated, including nucleic acid (DNA and RNA) approaches, virus-like particles (VLP), recombinant proteins, peptides, viral vectors, live attenuated viruses, killed viruses.

Live, attenuated vaccines. These vaccines contain a version of the living virus, the closest thing to a natural infection. Despite the fact that they present many antigenic components and are very effective, people with weakened immune systems cannot receive live vaccines. Codagenix, Inc. announced a partnership with the Serum Institute of India, Ltd. to develop a live attenuated vaccine.

Inactivated vaccines, made by killing, the virus during the process of making the vaccine. They produce immune responses in different ways than live vaccines. Often, multiple doses are necessary to build immunity.

Subunit vaccines include only parts of the virus or bacteria, or subunits, instead of the entire virus.	
S protein	WRAIR/USAMRIID
	AJ Vaccines
	EpiVax/University of Georgia
	Sanofi Pasteur
S1 or RBD protein	Baylor College of Medicine
Subunit	iBio/CC-Pharming
	VIDO-InterVac, University of Saskatchewan
S-Trimer (Trimer-Tag)	Clover Biopharmaceuticals Inc./GSK
Molecular clamp stabilized Spike protein	University of Queensland/GSK
Full length S trimers/ nanoparticle + Matrix M	Novavax
gp-96 backbone	Heat Biologics/Univ. Of Miami
Adjuvanted microsphere peptide	University of Saskatchewan
Peptide	Vaxil Bio
Drosophila S2 insect cell expression systemVLPs	ExpreS2ion

RNA vaccines are new technology with high potency, short production cycles, low-cost manufacturing. Messenger RNA (mRNA) is a single-stranded RNA molecule; this vaccine avoids the risk of permanent integration into the host genome. Only 17 nucleic acid-based products were approved and about 2700 clinical trials were conducted. The use of messenger RNA (mRNA) is expanding due to such important advantages compared to plasmid DNA as transient expression, the absence of the need to penetrate the nucleus and, therefore, the risk of carcinogenesis and mutagenesis, usually associated with DNA, is significantly reduced. Translation of the coding protein begins immediately in the cytoplasm, both in mitotic and non-mitotic cells. Firstly, In Vitro Transcribed (IVT) mRNA need to attach to the surface of the cell, which can occur through electrostatic interactions. Cell binding can also be improved with ligands able to interact with specific cell surface receptors. Then mRNA still has to cross the cytoplasmic membrane, diffuse the cytoplasm to reach the ribosomes. The main mechanism of cell entry is endocytosis. Endosomes mature and fuse with lysosomes, where the acidic environment and the presence of hydrolytic enzymes can degrade the nucleic acid. For successful vaccination, mRNA must avoid degradation. Nanosystems are designed to protect the mRNA and to overcome the barriers. Chemical carriers form complexes with the mRNA and vary in composition, size, shape, including lipidic, polymeric and polypeptidic systems,

dendrimers, gold nanoparticles, and hybrid systems. Lipid-based vectors are among the most widely used carriers. Lipid nanoparticles (LNPs) are the leading non-viral delivery system for mRNA that effectively protect from nucleases, deliver and release into the cytoplasm. A synthetic IVT mRNA consists of the following five fundamental structures, which can be chemically modified: Cap, open reading frame (ORF) encoding the desired protein, regulatory untranslated regions (UTRs), and optionally, to a polyadenylated tail (poly(A) tail).

Cap is a combination of inverted 7-methylguanosine with the first mRNA nucleotide. Cap0 protects the mRNA and initiate the translation. Uncapped mRNAs are immediately digested by nucleases. Cytosolic decapping enzymes can remove the mRNA cap. To achieve mRNA resistance to these enzymes, modified cap analogs, such as phosphorothioate, imidiphosphate, boranophosphate, etc., can be used.

The length of the polyadenylated tail affects the translation efficiency of mRNA.The presence of an internal ribosomal entry site (IRES) in the regulatory untranslated regions (UTR) allows mRNA to connect to the ribosome and initiates translation independent of the cap.

RNA vaccines	
Lipid nanoparticles(LNP)-encapsulated mRNA	Moderna/NIAID
LNP mRNA mixture encoding VLP LNP mRNA encoding RBD	Fudan University/Shanghai JiaoTong University/RNACure Biopharma
messenger RNA (mRNA)	China CDC/Tongji University/Stermina
	Arcturus/Duke-NUS
	BioNTech/Fosun Pharma/Pfizer
	Curevac
small activating RNA (saRNA)	Imperial College London

DNA vaccines usually consist of plasmid DNA molecules encoding one or more antigens. They need to enter the nucleus that may bring in the risk of integration and mutations in the human cells.	
DNA plasmid vaccine Electroporation device	Inovio Pharmaceuticals
DNA	Takis/Applied DNA Sciences/Evvivax
DNA plasmid vaccine	Zydus Cadila

Currently, about 70% of the clinical trials with nucleic acids use recombinant viruses as delivery systems, such as retroviruses, lentiviruses, adenoviruses and others.

Non-Replicating Viral Vector. They are combining the strong immunogenicity of live attenuated vaccines and the safety of subunit vaccines.	
MVA encoded VLP	GeoVax/BravoVax
Ad26 (alone or with MVA boost)	Janssen Pharmaceutical Companies
ChAdOx1	University of Oxford
adenovirus-based NasoVAX expressing spike protein	Altimmune
Ad5 S (GREVAX™ platform)	Greffex
Oral Vaccine platform	Vaxart

Replicating Viral Vector. By imitating a natural infection provide a complete cellular and antibody immune response. Although initial dose can be reduced by 2–3 times, the carrier will infect many more cells.	
Measles Vector	Zydus Cadila
Measles Vector	Institute Pasteur/Themis/Univ. of Pittsburg Center for Vaccine Research
TNX-1800. Horsepox vector expressing S protein	Tonix Pharma/Southern Research

In order for the vaccine to be approved, it must successfully pass several stages of research: preclinical (in vitro and in animals) and the three phases of clinical trials on volunteers are safety, dose, effectiveness testing. At present time there are 78 confirmed active projects, 73 are currently at exploratory or preclinical stages.

COVID-19: candidate vaccines in Clinical trials				
Vaccine candidate (developer/sponsor)	**Technology**	**Phase of trial (participants)**	**Location Duration**	**URL**
Ad5-nCoV (CanSino Biologics)	recombinant adenovirus type 5 vector	Phase II interventional trial (500) Phase I (108)	Wuhan, China 03/2020-12/2020	https://clinicaltrials.gov/ct2/show/NCT04313127
ChAdOx1 nCoV-19 (University of Oxford)	adenovirus vector	Phase I-II, randomized, placebo-controlled, multiple sites (510)	England 04/2020-05/2021	http://www.ox.ac.uk/news/2020-03-27-oxford-covid-19-vaccine-programme-opens-clinical-trial-recruitment
mRNA-1273 (Moderna, Cambridge, MA US NIAID)	lipid nanoparticle dispersion containing messenger RNA	Phase I (45)	United States 03/2020-06/2021	https://clinicaltrials.gov/ct2/show/NCT04283461
Pathogen-specific aAPC (Shenzhen Geno-Immune Medical Institute)	Artificial Antigen-Presenting Cells modified with lentiviral vector expressing synthetic minigene based on domains of selected viral proteins	Phase I (100)	Shenzhen, China 03/2020-2023	https://clinicaltrials.gov/ct2/show/NCT04299724
LV-SMENP-DC (Shenzhen Geno-Immune Medical Institute)	Dendritic Cells modified with lentiviral vector expressing synthetic minigene based on selected viral proteins; administered with antigen-specific cytotoxic T lymphocyte	Phase I (100)	Shenzhen, China 03/2020-2023	https://clinicaltrials.gov/ct2/show/NCT04276896
INO-4800 (Inovio Pharmaceuticals, CEPI)	DNA plasmid encoding S protein delivered by electroporation	Phase I (40)	United States 04/2020-11/2020	https://clinicaltrials.gov/ct2/show/record/NCT04336410

Look updated list of vaccines on COVID-19 vaccine tracker

https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker

The vaccine is unlikely to be available sooner than 6 months after the start of clinical trials. It will most likely take weeks to vaccinate a large part of the population, and the second dose of the vaccine will be needed after 3-4 weeks. Protective immunity is likely to be achieved only 1-2 weeks after the second vaccination. Due to frequent mutations of the virus, do not guarantee that infection will not occur. Another consideration is the attenuation of antibody responses, the re-infection of an individual with the same virus is possible. Antibody titers in people who recovered from SARS-CoV-1 or MERS-CoV infections were often initially weak or decreased after 2–3 years. An effective SARS-CoV-2 vaccine will have to overcome these challenges in which the virus causes periodic epidemics.

Correlation with BCG vaccination

The disease has spread in most countries of the world with great speed. The percentage of people infected and those who died from the disease differs in countries. Studies from New York Institute of Technology shows a direct correlation between mortality rates demonstrated by countries with compulsory and optional Bacillus Calmette-Guérin vaccination. For reliability, low-income countries were excluded from further analysis because there was a problem with the understatement of case data. BCG vaccination has been shown to provide broad protection against viral infections and correlate with a decrease in cases of COVID-19.

Epidemiologists from the University of Texas conducted an even larger study, examining the statistics of 178 countries, and came to the same conclusion. According to their estimates, the number of infected per capita in countries with compulsory vaccination against tuberculosis is about ten times lower, and Covid-19 victims are 20 times lower.

Danes Peter Aabi and Christina Stabel Benn, working in Guinea-Bissau, have studied the side effects of vaccination for many years and assert that BCG provides effective protection against many diseases, strengthening the immune system as a whole. According to their studies, which have been going on for several decades, people vaccinated with BCG become on average 30% less susceptible to all bacterial, fungal and viral infections known to science. BCG also reduce bladder cancer and Buruli ulcer.

VPM1002 vaccine based on BCG will be studied in hospitals throughout Germany. The study will be conducted by the Max Planck Institute for Biology of Infection in Berlin. Researchers in Australia are also starting BCG vaccine trials for COVID-19. About 4,000 healthcare providers will participate in this study.

Conclusion

As a rule, the development of new vaccines usually takes at least 10 years, during which they evaluate the effectiveness and safety of the vaccine. Although vaccine development is very slow, it is necessary and urgent, so experience with the use of vaccines against SARS and MERS strains are being used.

Different companies are working to develop a vaccine against the virus. Johnson & Johnson plans to begin clinical trials in humans by September 2020. Inovio Pharmaceuticals has already conducted experiments with the INO-4800 vaccine in the clinic. More than 2,000 patients receive the INOVIO DNA test vaccine intramuscularly or intradermally using the CELLECTRA® smart device, which can open small pores in the cell with a short electrical pulse that allows plasmids to penetrate. The results of clinical trials showed that the vaccine caused a high level of antibody responses in 95% of patients, and an increased number of immune T cells in almost 90% of the study participants. The long-lasting antibody responses to its DNA vaccine INO-4700 were for 60 weeks. On April 10, CanSino launched its Phase II trial of Ad5-nCoV, involving 500 healthy adults, to evaluate the immunogenicity and safety of vaccine. The first phase has already passed successfully, but data has not yet been published. Ad5-nCoV is a genetically engineered vaccine candidate with the replication-defective adenovirus type 5 as the vector to express SARS-CoV-2 spike protein. Moderna, Pfizer, and BioNTech are moving at tremendous speed in the development of RNA vaccines.

If a vaccine were to become available in the next year, several billion people will need it, but no one manufacturer has such production capacities, so at first, it will be available to medical staff, pregnant women, children with preexisting conditions, higher-risk patients and people over the age of 65.

More and more research institutions in different countries have announced their SARS-CoV-2 vaccine development program. We hope that a safe and effective vaccine will be available soon.

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