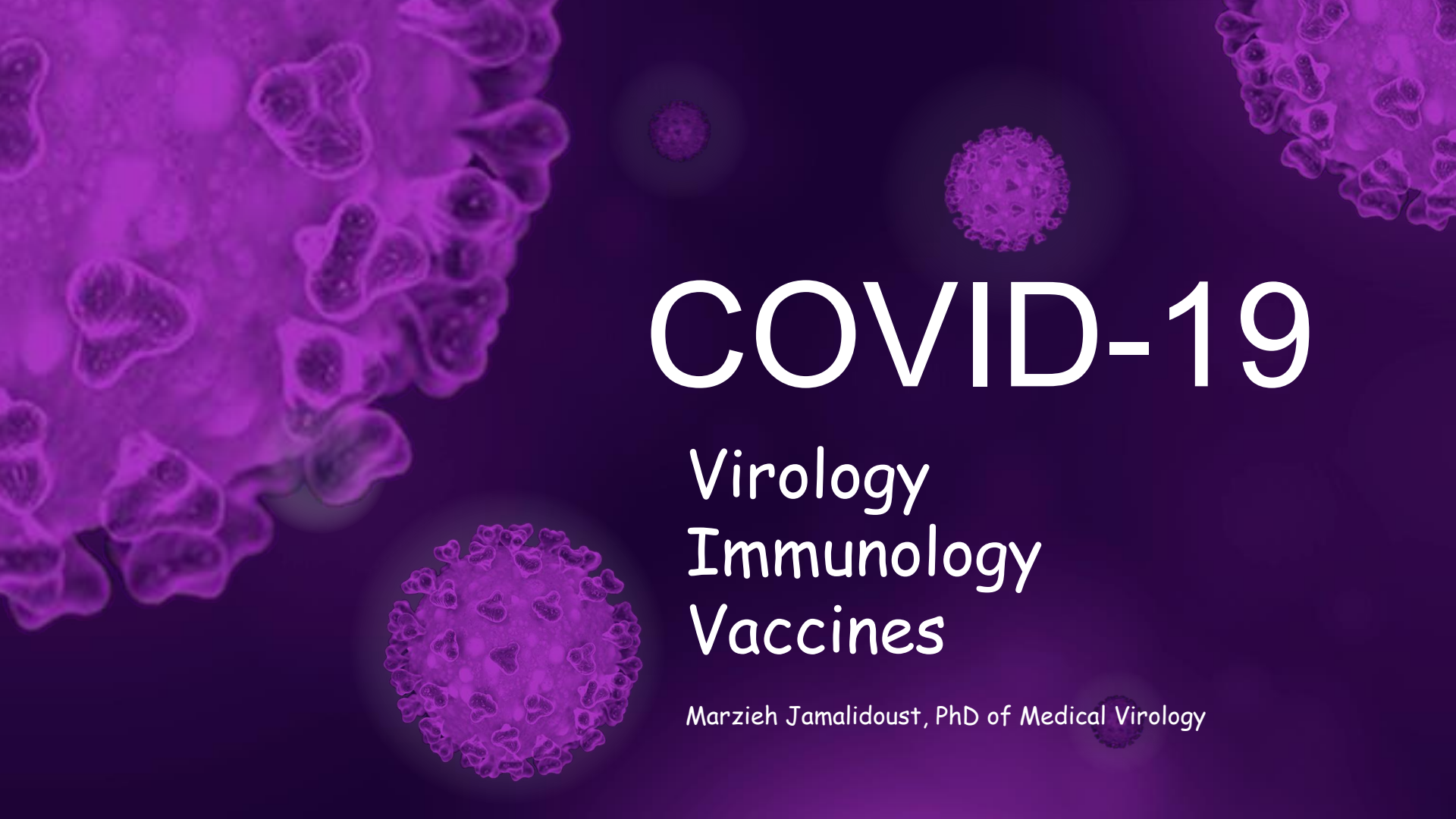
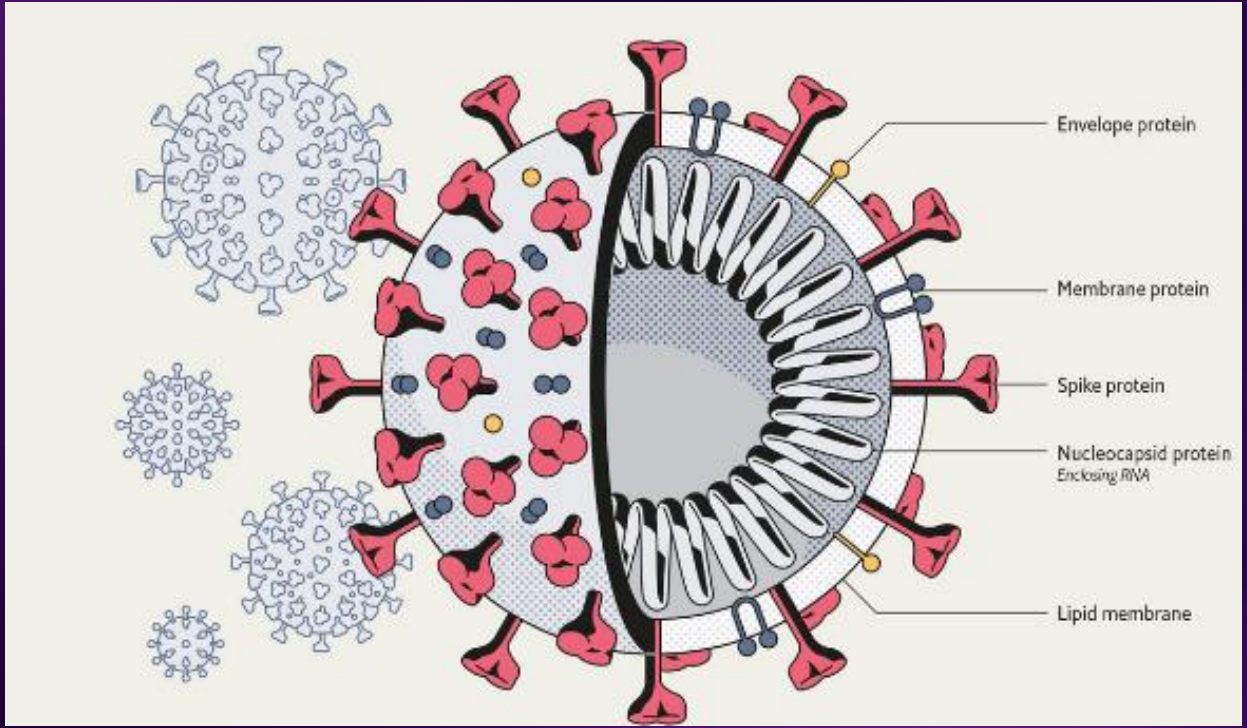


COVID-19

Virology
Immunology
Vaccines

Marzieh Jamalidoust, PhD of Medical Virology

Virology


Envelope protein
Membrane protein
Spike protein
Nucleocapsid protein
Enclosing RNA
Lipid membrane

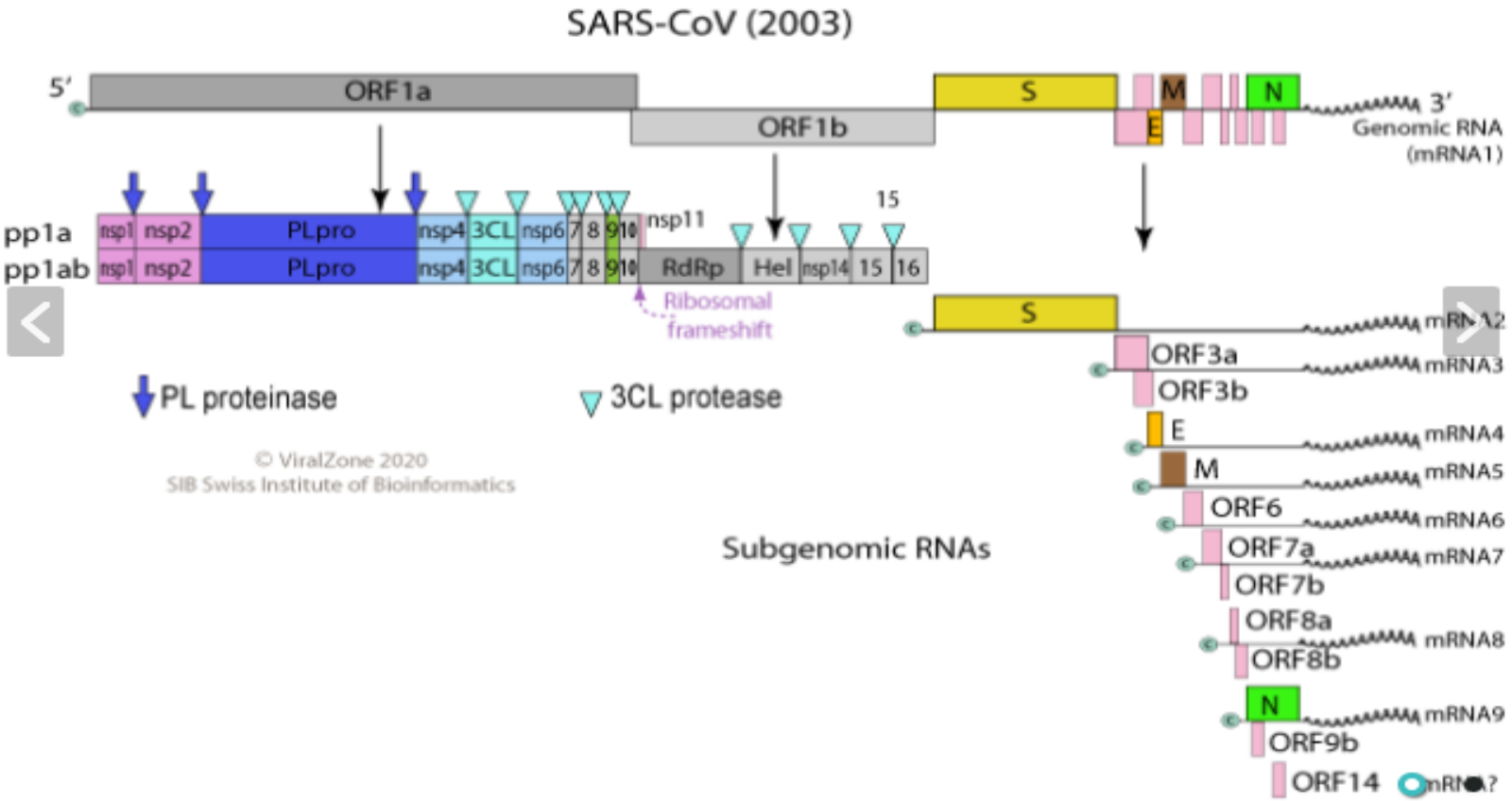
01.

positive-sense, single-stranded enveloped RNA viruses with helical capsids that infect a wide range of hosts including humans, bats, other mammals, and birds.

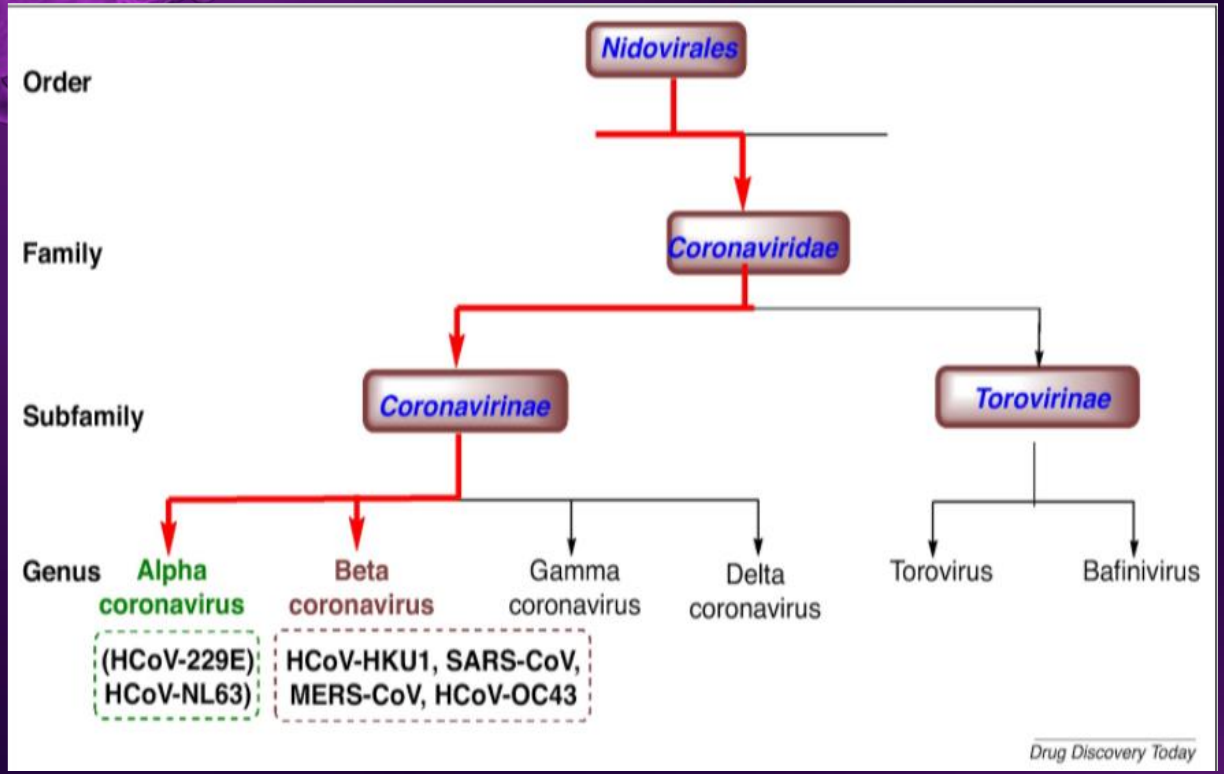
02.

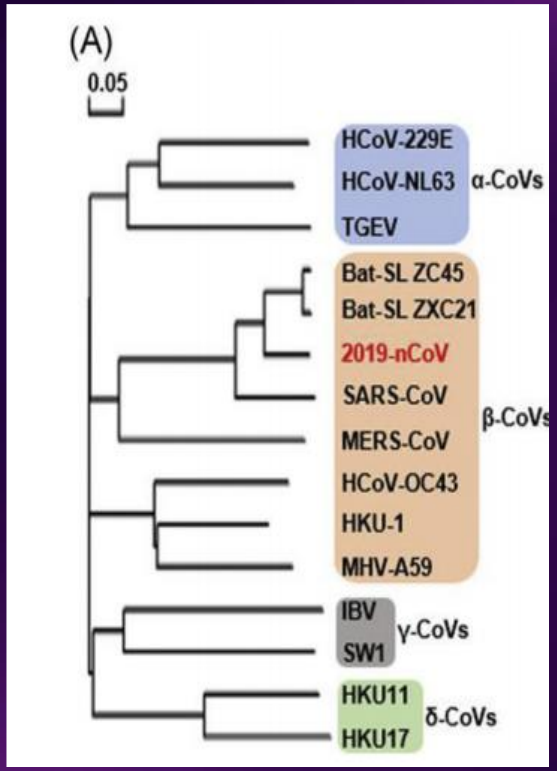
The host receptor for SARS-CoV-2 cell entry is the same as for SARS-CoV, the angiotens in-converting enzyme 2 (ACE2). The cellular protease TMPRSS2 also appears important for SARS-CoV-2 cell entry.

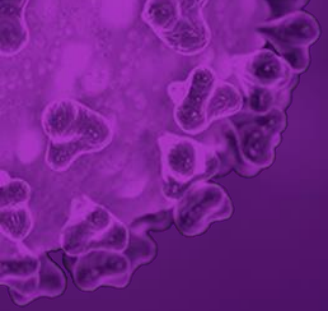
GENOME



Monopartite, linear ssRNA(+) genome of 27-32kb in size (the largest of all RNA virus genomes). Capped, and polyadenylated. The leader RNA (65-89 bp) at the 5' end of the genome is also present at the end of each subgenomic RNAs.


Order
Nidovirales
Family
Coronaviridae
Subfamily
Coronavirinae
Torovirinae
Genus
Alpha coronavirus
Beta coronavirus
Gamma coronavirus
Delta coronavirus
Torovirus
Bafinivirus
(HCoV-229E) HCoV-NL63)
HCoV-HKU1, SARS-CoV, MERS-CoV, HCoV-OC43
Drug Discovery Today


(A)
0.05
HCoV-229E
HCoV-NL63
TGEV
α-CoVs
Bat-SL ZC45
Bat-SL ZXC21
2019-nCoV
SARS-CoV
MERS-CoV
HCoV-OC43
HKU-1
MHV-A59
β-CoVs
IBV
SW1
γ-CoVs
HKU11
HKU17
δ-CoVs

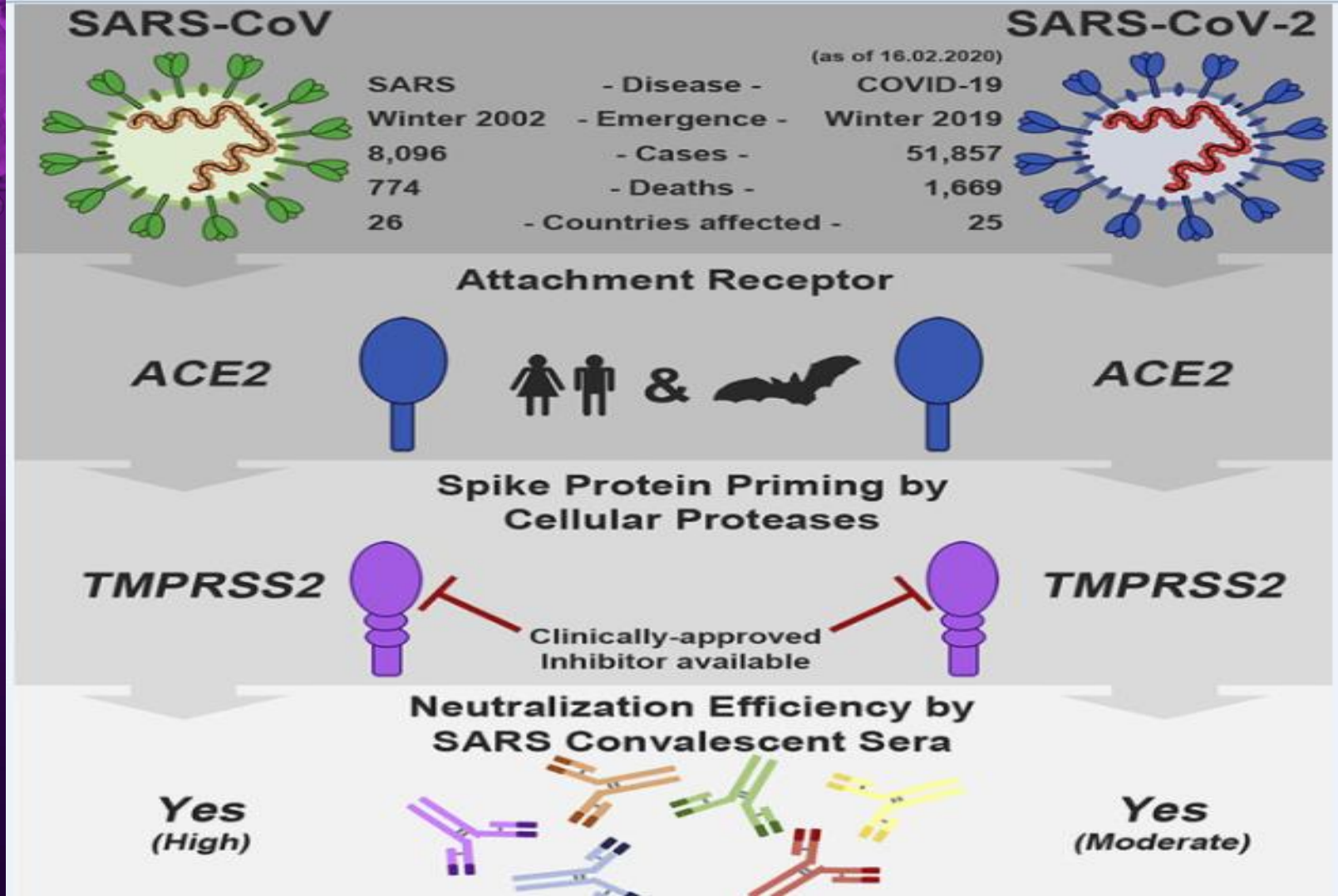


1. entry requires S protein priming by cellular proteases, which entails S protein cleavage at the S1/S2 and the S2′ site and allows fusion of viral and cellular membranes, a process driven by the S2 subunit.

2. SARS-S engages angiotensin-converting enzyme 2 (ACE2) as the entry receptor (Li et al., 2003) and employs the cellular serine protease TMPRSS2 for S protein priming.

3. The SARS-S/ACE2 interface has been elucidated at the atomic level, and the efficiency of ACE2 usage was found to be a key determinant of SARS-CoV transmissibility (Li et al., 2005a, 2005b).

4. SARS-S und SARS-2-S share 76% amino acid identity. The Cellular Serine Protease TMPRSS2 Primes SARS-2- S for Entry, and a Serine Protease Inhibitor Blocks SARS-CoV-2 Infection of Lung Cells.


SARS-CoV
SARS-CoV-2
(as of 16.02.2020)
SARS
- Disease -
COVID-19
Winter 2002
- Emergence -
Winter 2019
8,096
- Cases -
51,857
774
- Deaths -
1,669
26
- Countries affected -
25
Attachment Receptor
ACE2
&
ACE2
Spike Protein Priming by
Cellular Proteases
TMPRSS2
Clinically-approved
Inhibitor available
TMPRSS2
Neutralization Efficiency by
SARS Convalescent Sera
Yes
(High)
Yes
(Moderate)

SARS-CoV-2 origin

Archives of Virology (2020) 165:2341–2348
https://doi.org/10.1007/s00705-020-04750-z

BRIEF REPORT

A palindromic RNA sequence as a common breakpoint contributor to copy-choice recombination in SARS-COV-2

William R. Gallaher[1,2]

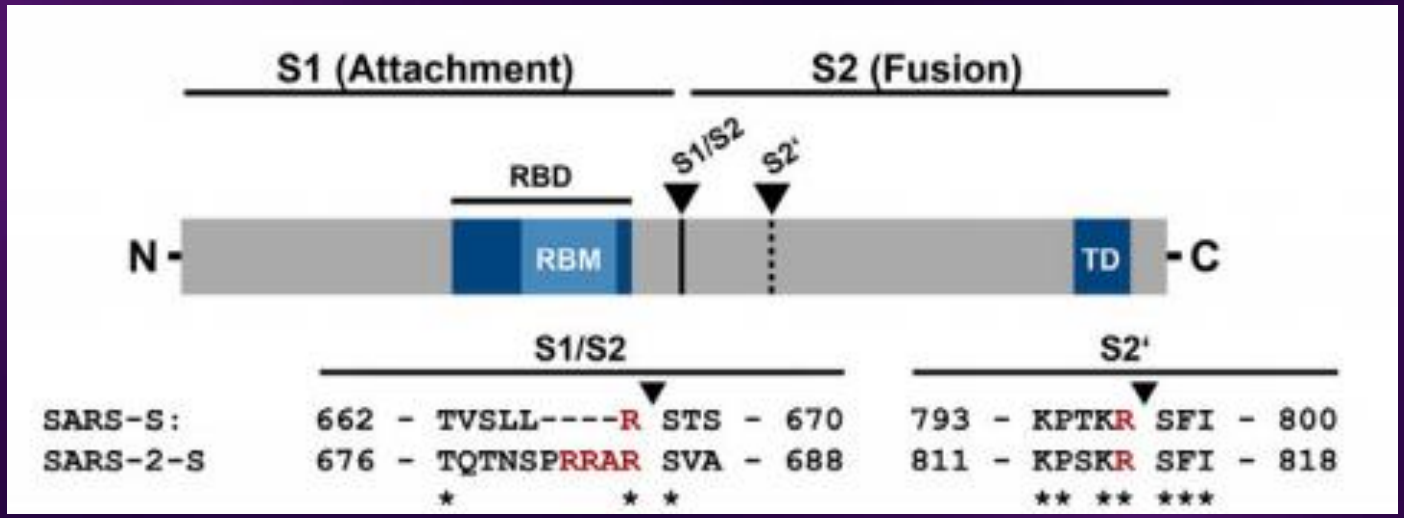
Received: 5 June 2020 / Accepted: 20 July 2020 / Published online: 31 July 2020

Abstract
Much remains unknown concerning the origin of the novel pandemic coronavirus that has raged across the globe since emerging in Wuhan of Hubei province, near the center of the People's Republic of China, in December of 2019. All current members of the family *Coronaviridae* have arisen by a combination of incremental adaptive mutations, against the backdrop of many recombinational events throughout the past, rendering each a unique mosaic of RNA sequences from diverse sources. The consensus among virologists is that the base sequence of the novel coronavirus, designated SARS-CoV-2, was derived from a common ancestor of a bat coronavirus, represented by the strain RaTG13, isolated in Yunnan province in 2013. Into that ancestral genetic background, several recombination events have since occurred from other divergent bat-derived coronaviruses, resulting in localized discordance between the two. One such event left SARS-CoV-2 with a receptor binding domain (RBD) capable of binding the human ACE-2 receptor lacking in RaTG13, and a second event uniquely added to SARS-CoV-2 a site specific for furin, capable of efficient endoproteolytic cleavage and activation of the spike glycoprotein responsible for virus entry and cell fusion. This paper demonstrates by bioinformatic analysis that such recombinational events are facilitated by short oligonucleotide "breakpoint sequences", similar to CAGAC, that direct recombination naturally to certain positions in the genome at the boundaries between blocks of RNA code and potentially RNA structure. This "breakpoint sequence hypothesis" provides a natural explanation for the biogenesis of SARS-CoV-2 over time and in the wild.

1. In that spirit, on January 24, scientists at the Wuhan Institute of Virology (WIV) published the sequence of a viral isolate obtained from the bat species Rhinolophus affinis in 2013, designated Bat_RaTG13, which **was 96% identical to SARS-CoV-2, with an even higher degree of amino acid sequence identity.**

2. This paper demonstrates by bioinformatic analysis that such recombinational events are facilitated by short oligonucleotide "breakpoint sequences", similar to CAGAC, that direct recombination naturally to certain positions in the genome at the boundaries between blocks of RNA code and potentially RNA structure.

3. Investigators at WIV had previously participated in "gain of function" experiments to probe how bat coronaviruses from the wild could acquire functions permitting human infection [16, 17].


S1 (Attachment)
S2 (Fusion)
RBD
S1/S2
S2'
N
RBM
TD
C
S1/S2
S2'
SARS-S: 662 - TVSLL----R STS - 670 793 - KPTKR SFI - 800
SARS-2-S 676 - TQTNSPRRAR SVA - 688 811 - KPSKR SFI - 818

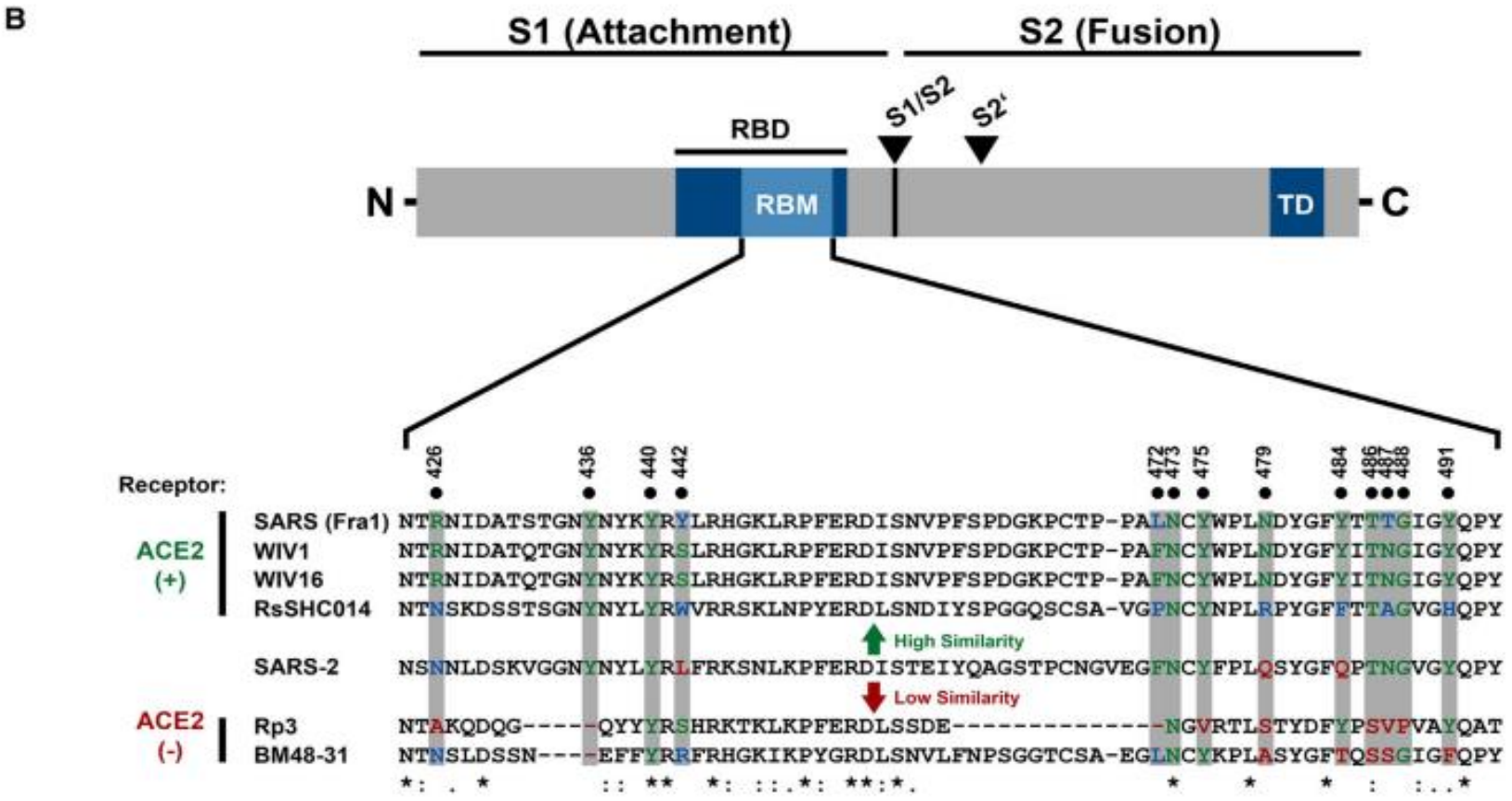


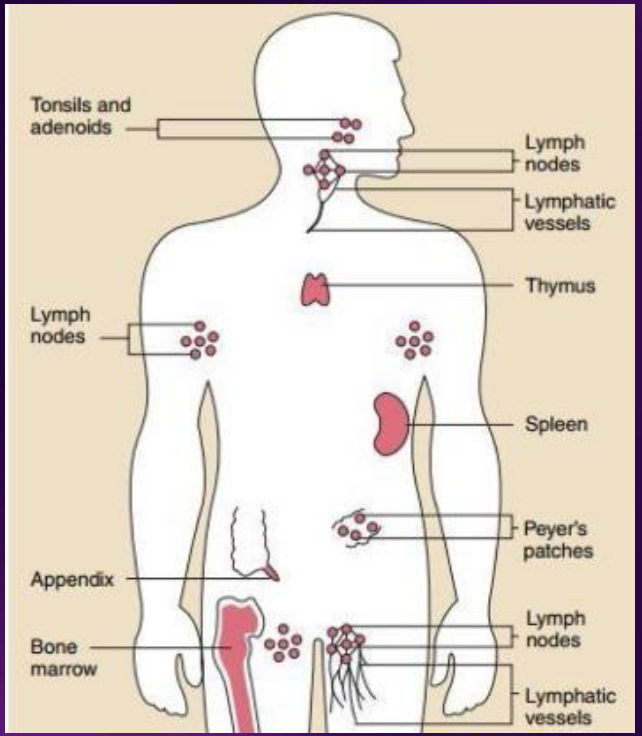
Figure 2. SARS-2-S Harbors Amino Acid Residues Critical for ACE2 Binding

(A) The S protein of SARS-CoV-2 clusters phylogenetically with S proteins of known bat-associated betacoronaviruses (see Figure S2 for more details).

(B) Alignment of the receptor binding motif of SARS-S with corresponding sequences of bat-associated betacoronavirus S proteins, which are able or unable to use ACE2 as cellular receptor, reveals that SARS-CoV-2 possesses crucial amino acid residues for ACE2 binding.

Immunology

the key player in the immune system is the white blood cells, which can travel throughout the body through the blood vessels.
To monitor for invading microbes, the body exchanges cells and fluids between blood and lymphatic vessels and enables the lymphatic system.



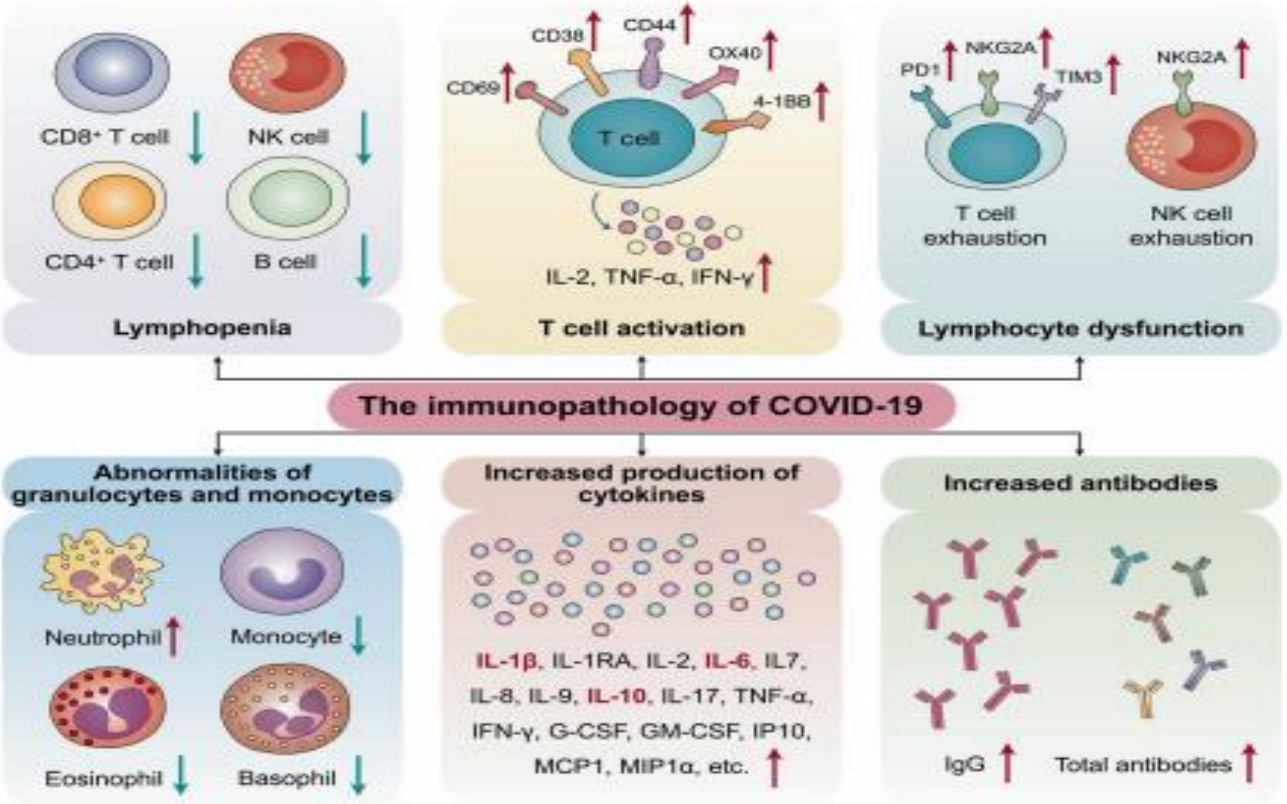


Fig. 1 The immunopathology of COVID-19. The immune patterns of COVID-19 include lymphopenia, lymphocyte activation and dysfunction, abnormalities of granulocytes and monocytes, increased production of cytokines, and increased antibodies. Lymphopenia is a key feature of patients with COVID-19, especially in severe cases. CD69, CD38, and CD44 are highly expressed on $CD4^+$ and $CD8^+$ T cells of patients, and virus-specific T cells from severe cases exhibit a central memory phenotype with high levels of IFN-γ, TNF-α, and IL-2. However, lymphocytes show an exhaustion phenotype with programmed cell death protein-1 (PD1), T cell immunoglobulin domain and mucin domain-3 (TIM3), and killer cell lectin-like receptor subfamily C member 1 (NKG2A) upregulation. Neutrophil levels are significantly higher in severe patients, while the percentage of eosinophils, basophils, and monocytes are reduced. Increased cytokine production, especially of IL-1β, IL-6, and IL-10, is another key characteristic of severe COVID-19. IgG levels are also increased and there is a higher titer of total antibodies

Lymphopenia

- Patients also show a marked reduction in CD4+ T, CD8+ T, NK, and B cell number.
- Lymphocyte percentages were found to be lower than 20% in severe cases.
- Further analysis showed a significant decrease in T cell counts, especially CD8+ T cells in severe cases compared with mild cases.
- the percentage of memory helper T cells (CD3+CD4+CD45RO+) is also decreased in severe cases compared with non-severe cases.
- Impaired B cells are not as significant as impaired T or NK cells

- most patients infected with microbe had low lymphocyte levels, indicating that patients with lymphopenia are more prone to microbial infection.

Lymphocyte activation and dysfunction

- the CD8+ T cell response occurred more frequently than the CD4+ T cell response.
- CD69, CD38, and CD44 are highly expressed on CD4+ and CD8+ T cells of patients with COVID-19 compared with healthy control
- Another study also demonstrated that activated CD4+ and CD8+ T cells are present in the blood before the relief of symptoms.
- In addition, T cells in patients with COVID-19 show exhaustion phenotypes. (programmed cell death protein-1 and T cell immunoglobulin domain and mucin domain-3 levels on CD8+ T cells are increased in overtly symptomatic stages compared with the prodromal stage, and peak levels are detected in severe conditions)

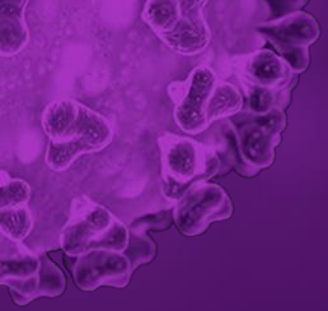
Abnormalities of granulocytes and monocytes

- The number of granulocytes and monocytes is also abnormal in patients with COVID-19. Neutrophils and the neutrophil-to lymphocyte ratio—usually important indicators for severe cases and poor clinical outcome—are significantly higher in severe patients than in non-severe patients.

- a reduced percentage of eosinophils, basophils, and monocytes was observed in severe patients.

Increased production of cytokines

- Most severe COVID-19 cases exhibit an extreme increase in inflammatory cytokines, including IL-1β, IL-2, IL-6, IL-7, IL-8, IL-10, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), interferon inducible protein-10 (IP10), monocyte chemotactic protein 1 (MCP1), macrophage inflammation protein-1α, IFN-γ, and TNF-α, representing a “cytokine storm”.



- A cytokine storm can initiate viral sepsis and inflammatory-induced lung injury, leading to ARDS, respiratory failure, shock, organ failure, and potentially death
- Continuous high levels of cytokines (CXCL10, CCL7, and IL-1RA) are associated with lung dysfunction and injury as well as fatal outcomes.
- severe syndromes of multiple organ dysfunction are closely correlated with elevated cytokine levels, which could be utilized as a promising therapeutic or prevention target for patients with COVID-19 and severe syndromes.

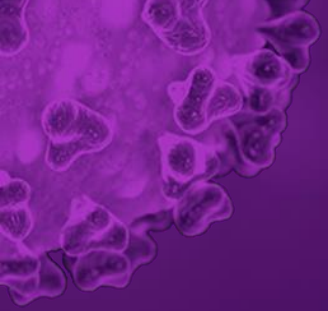
Herd immunity

Vaccines are an effective way for a population to achieve what is known as “**herd immunity**.” This is the concept that the pandemic will end once **approximately 60-70 per cent** of people become immune to SARS-CoV-2.

An alternative is to let SARS-CoV-2 run its natural course until herd immunity is achieved. With physical distancing, some epidemiologists argue this **could take two years**, during which time a vaccine could be developed.

However, vaccinating at the tail end of a pandemic when disease incidence is very low and declining may be of little utility, hence the race to develop a vaccine for COVID-19.
If one is not in widespread use within the first half of 2021, it will probably be too late to have a meaningful impact on control of COVID-19.

Vaccines

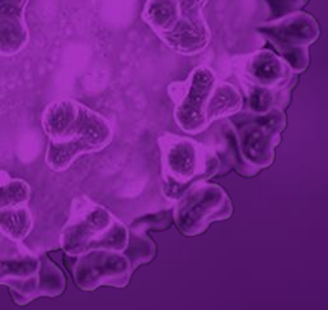


Immunization currently prevents 2-3 million deaths every year from diseases like diphtheria, tetanus, pertussis, influenza and measles.

There are now vaccines to prevent more than 20 life-threatening diseases, and work is ongoing at unprecedented speed to also make COVID-19 a vaccine-preventable disease.

There are currently more than 100 COVID-19 vaccine candidates under development, with a number of these in the human trial phase.

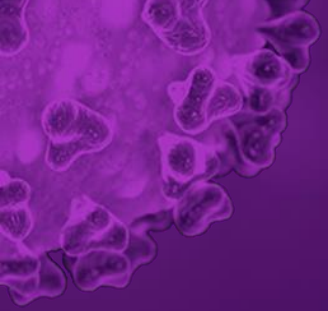
WHO is working in collaboration with scientists, business, and global health organizations through the ACT Accelerator to speed up the pandemic response. When a safe and effective vaccine is found, **COVAX** (led by WHO, GAVI and CEPI) will facilitate the equitable access and distribution of these vaccines to protect people in all countries. People most at risk will be prioritized.



The fact is, no vaccine against a coronavirus has successfully navigated the rigours of clinical testing, despite having up to 17 years to do so.

The same applies to other dangerous respiratory pathogens, such as respiratory syncytial virus

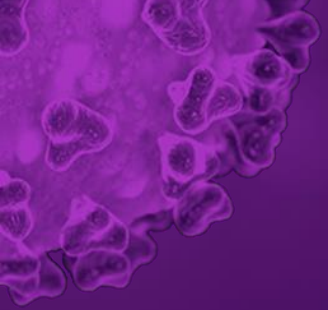
One concern is that some vaccines can protect against disease (that is, the outcome of an infection) but not against infection (the ability of the virus to get into the body). In this scenario, vaccinated individuals could potentially become asymptomatic carriers of SARS-CoV-2, thereby spreading COVID-19. For this and many other reasons, a cautious approach must be taken to developing COVID-19 vaccines.



many of the vaccine technologies that can most readily make it to the front of the line are not necessarily the best quality.

The easiest way to make a vaccine is to inactivate the pathogen or use pieces of it, and mix them with an adjuvant, which tells the immune system that the pathogen is dangerous and worth responding to

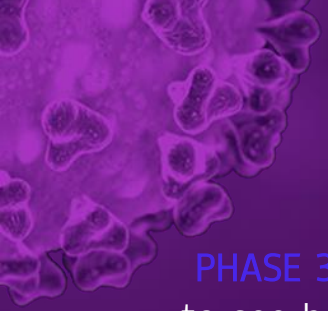
However, an inactivated virus or its components do not behave like the live virus, so the immune system sometimes responds to these vaccines in a way that is ineffective or sometimes even dangerous. For example, no vaccine based on the genetic material, known as ribonucleic acid or RNA, from a virus like SARS-CoV-2 has ever been approved.
Further, some vaccines developed against the original SARS-CoV, after the epidemic was over, exacerbated the disease in mice.



PRECLINICAL TESTING: Scientists test a new vaccine on cells and then give it to **animals** such as mice or monkeys to see if it produces an immune response. We have confirmed 89 preclinical vaccines in active development.

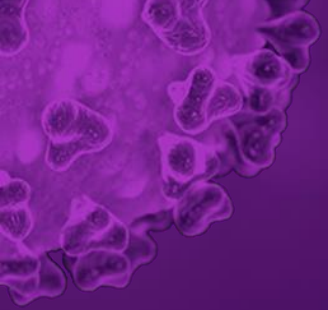
PHASE 1 SAFETY TRIALS: Scientists give the vaccine to a **small number of people** to test safety and dosage as well as to confirm that it stimulates the immune system.

PHASE 2 EXPANDED TRIALS: Scientists give the vaccine to **hundreds of people** split into groups, such as children and the elderly, to see if the vaccine acts differently in them. These trials further test the vaccine's safety and ability to stimulate the immune system.



PHASE 3 EFFICACY TRIALS: Scientists give the vaccine to **thousands of people** and wait to see how many become infected, compared with volunteers who received a placebo. These trials can determine if the vaccine protects against the coronavirus.
In June, the F.D.A. advised vaccine makers that they would want to see evidence that vaccines can protect at least 50 percent of those who receive it. In addition, Phase 3 trials are large enough to reveal evidence of relatively rare side effects that might be missed in earlier studies.

EARLY OR LIMITED APPROVAL: China and Russia have approved vaccines without waiting for the results of Phase 3 trials. Experts say the rushed process has serious risks.



APPROVAL: Regulators in each country review the trial results and decide whether to approve the vaccine or not. During a pandemic, a vaccine may receive emergency use authorization before getting formal approval. Once a vaccine is licensed, researchers continue to monitor people who receive it to make sure it's safe and effective.

COMBINED PHASES: One way to accelerate vaccine development is to combine phases. Some coronavirus vaccines are now in Phase 1/2 trials, for example, in which they are tested for the first time on hundreds of people. (Note that our tracker counts a combined Phase 1/2 trial as both Phase 1 and Phase 2.)

PAUSED: If investigators observe worrying symptoms in volunteers, they can put a trial on pause. After an investigation, the trial may resume or be abandoned.

Genetic Vaccines

Vaccines that deliver one or more of the coronavirus's own genes into our cells to provoke an immune respons

PHASE 3

moderna

NIH National Institutes of Health
Turning Discovery Into Health

PHASE 2

Zydus
dedicated to life

PHASE 2 PHASE 3 COMBINED PHASES

BIONTECH Pfizer FOSUN PHARMA

PHASE 2

CUREVAC

PRECLINICAL

SANOFI

Translate BIO

PHASE 1 PHASE 2 COMBINED PHASES

Imperial College London

MORNINGSIDE

PHASE 1 PHASE 2 COMBINED PHASES

ARCTURUS therapeutics

DukeNUS Medical School

PHASE 1 PHASE 2 COMBINED PHASES

AnGes

大阪大学 OSAKA UNIVERSITY

TaKaRa

PHASE 1 PAUSED

INOVIO

POWERING DNA MEDICINES

PHASE 1

Genexine

PHASE 1

ABOGEN

WALVAX 沃森生物
WALVAX BIOTECHNOLOGY CO., LTD.

PHASE 1

entos

PHASE 1

Chula
Chulalongkorn University

Chula VRC
Chula Vaccine Research Center
ศูนย์เชี่ยวชาญเฉพาะทางการวิจัยและพัฒนาวัคซีน จุฬาลงกรณ์มหาวิทยาลัย

Viral Vector Vaccines

Vaccines that contain viruses engineered to carry coronavirus genes. Some viral vector vaccines enter cells and cause them to make viral proteins. Other viral vectors slowly replicate, carrying coronavirus proteins on their surface.

PHASE 3 APPROVED FOR LIMITED USE IN CHINA

CanSinoBIO

PHASE 3 PAUSED

Johnson & Johnson

Beth Israel Lahey Health

Beth Israel Deaconess Medical Center

PHASE 3 APPROVED FOR EARLY USE IN RUSSIA

МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РОССИЙСКОЙ ФЕДЕРАЦИИ

PHASE 1

REITHERA

SISTEMA SANITARIO REGIONALE

IRCCS LAZZARO SPALLANZANI

Protein-Based Vaccines

Vaccines that contain coronavirus proteins but no genetic material. Some vaccines contain whole proteins, and some contain fragments of them. Some pack many of these molecules on nanoparticles.

PHASE 3

NOVAVAX

Creating Tomorrow's Vaccines Today

PHASE 2

ZFSW

The Biologics Company

INSTITUTE OF MEDICAL BIOLOGY

CHINESE ACADEMY OF MEDICAL SCIENCES

PHASE 1 PHASE 2 COMBINED PHASES

APPROVED FOR EARLY USE IN RUSSIA

BEKTOP

PHASE 1 PHASE 2 COMBINED PHASES

IFV INSTITUTO FINLAY DE VACUNAS

PHASE 1 PHASE 2 COMBINED PHASES

SANOFI gsk

PHASE 1 PHASE 2 COMBINED PHASES

spybiotech

PHASE 1

三叶草生物制药 Clover Biopharmaceuticals gsk DYNAVAX INNOVATING IMMUNOLOGY

PHASE 1

THE UNIVERSITY OF QUEENSLAND AUSTRALIA CSL

Inactivated or Attenuated Coronavirus Vaccines

Vaccines created from weakened coronaviruses or coronaviruses that have been killed with chemicals.

PHASE 3 | APPROVED FOR LIMITED USE IN U.A.E.

SINOPHARM

武汉生物制品研究所有限责任公司

WUHAN INSTITUTE OF BIOLOGICAL PRODUCTS CO.,LTD.

PHASE 3

BHARAT BIOTECH

icmr INDIAN COUNCIL OF MEDICAL RESEARCH

NATIONAL INSTITUTE OF VIROLOGY PUNE

PHASE 3 | APPROVED FOR LIMITED USE IN CHINA

sinovac

PHASE 1 | PHASE 2 | COMBINED PHASES

Russian Academy of Sciences


VACCINE
Coronavirus
SARS-CoV-2
10 ml
VACCINE
Coronavirus
SARS-CoV-2
10 ml

THE END.