Emerging Coronavirus Diseases

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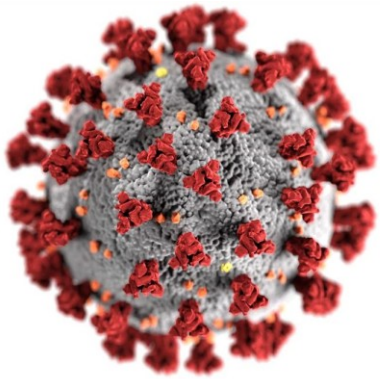
Principal points of the presentation

- Coronavirus family generally
- Severe Acute Respiratory Syndrome (SARS-CoV-1)
- Middle East Respiratory Syndrome (MERS-CoV)
- **COVID-19 (SARS-CoV-2)**
  - etiopathogenesis
  - clinical manifestations
  - diagnostics
  - **treatment options**
  - **prevention and control**



Coronaviridae

→ family of **enveloped**, single-strand, nonsegmented **RNA viruses**

→ circulate among **mammals and birds**, animal coronaviruses can rarely **spread to humans** and subsequently spread between people

2 humans serogroups (229E and OC43)

→ cause usually mild to moderate **respiratory illnesses** (1/3 of „common colds“)

→ able to survive in dry air for up to 3 hours, killed by exposure to UV light

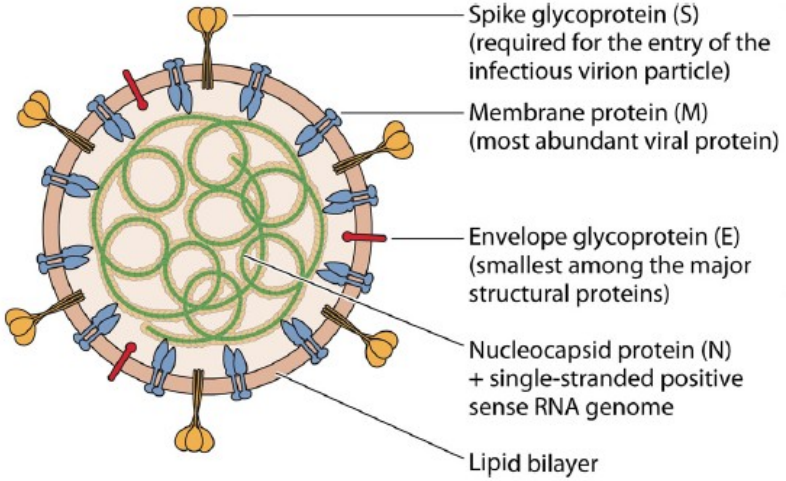
→ mutate easily, each mutation triggers off an epidemic of respiratory disease

→ bats are considered as **natural hosts** of these viruses

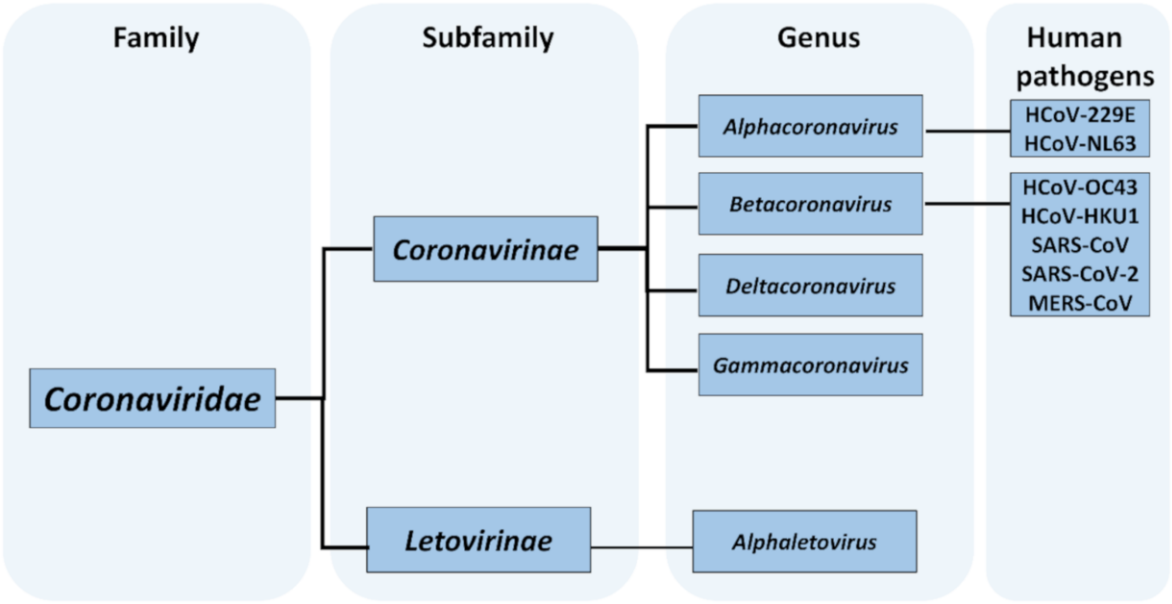
Virus structure

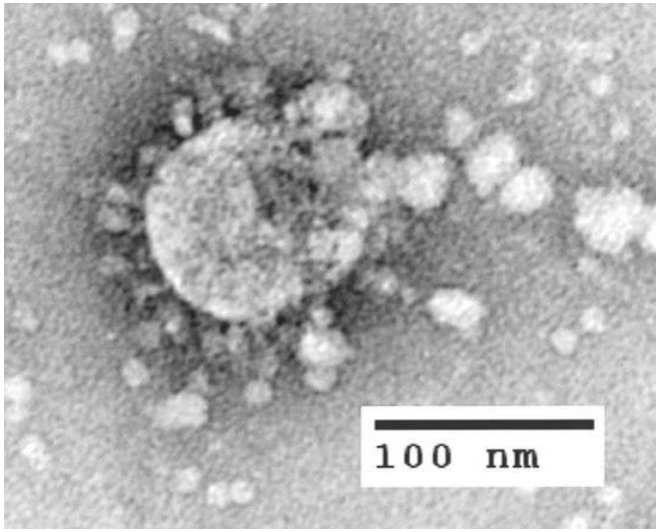
Envelope (lipid bilayer), **S** – spike protein,
M – membrane protein, **E** – envelope protein,
N – nucleocapsid with RNA

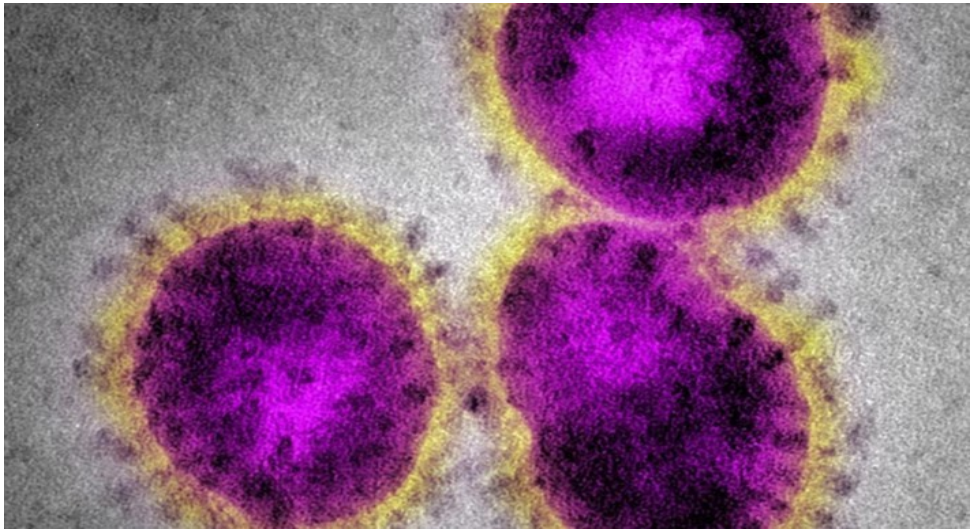
→ “coronavirus” refers to the protein molecules surrounding the virus, making it look like a **crown** (lat. „corona“)



Classification and Taxonomy of CoV







Severe Acute Respiratory Syndrome

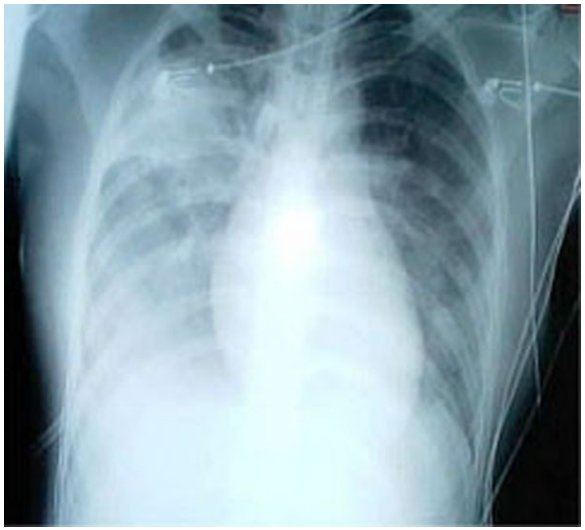
→ respiratory disease caused by SARS-associated coronavirus **(SARSr-CoV or SARS-CoV-1)**
→ first identified at the end of February 2003 during an outbreak in **China** and spread **(2003 – 2004)** to 4 other countries (Hong Kong, Taiwan, Canada, Singapore)
→ first severe and readily transmissible new infection to emerge in the 21st century and showed a clear capacity to spread along the routes of **international air travel**

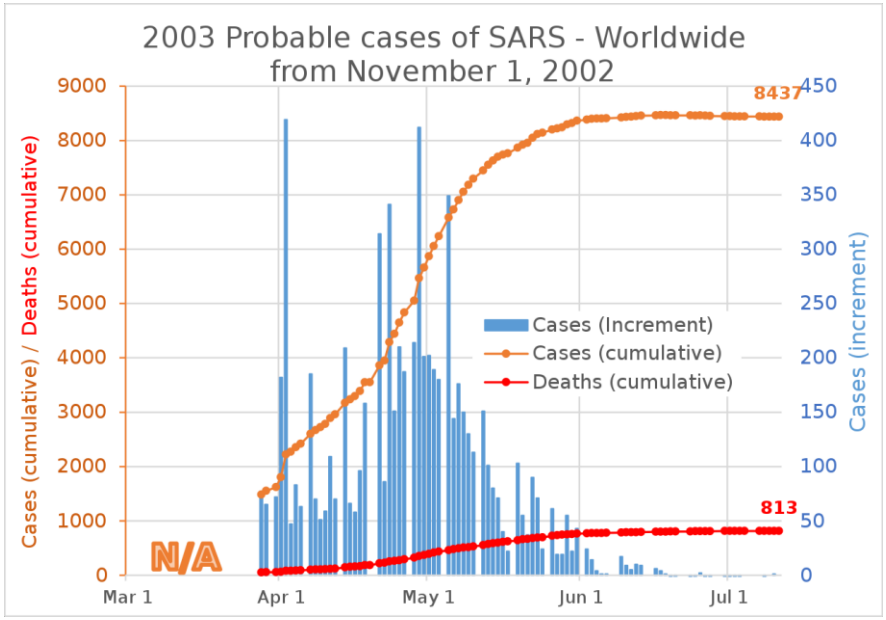
→ characteristic clinical symptoms include **fever above 38 °C**, muscle pain, lethargy, cough, sore throat, **complications** were direct viral or secondary bacterial **pneumonia**
→ in June 2003, the incidence was 8 422 cases with **a case fatality rate of 11 %**

→ **measurement of body temperature** at international airports, often using thermal imagers and subsequent targeted testing, was considered a key factor in stopping the spread of SARS-CoV-1

→ chinese scientists traced the virus through the intermediary of **Asian palm civets** to cave-dwelling **bats** in Yunnan (province in the **southwest China**)

Severe Acute Respiratory Syndrome





Middle East Respiratory Syndrome

→ viral respiratory infection caused by the **MERS-coronavirus** (MERS-CoV)

→ first identified case occurred in June 2012 in Jeddah, **Saudi Arabia**, generally most cases have occurred in the **Arabian Peninsula**

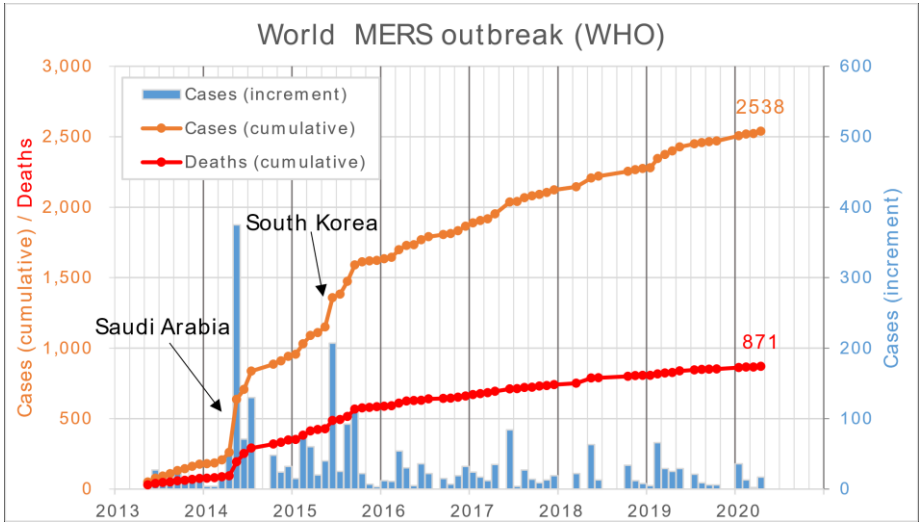
→ next outbreaks have occurred in **South Korea** (2015) and also in Saudi Arabia (2018)

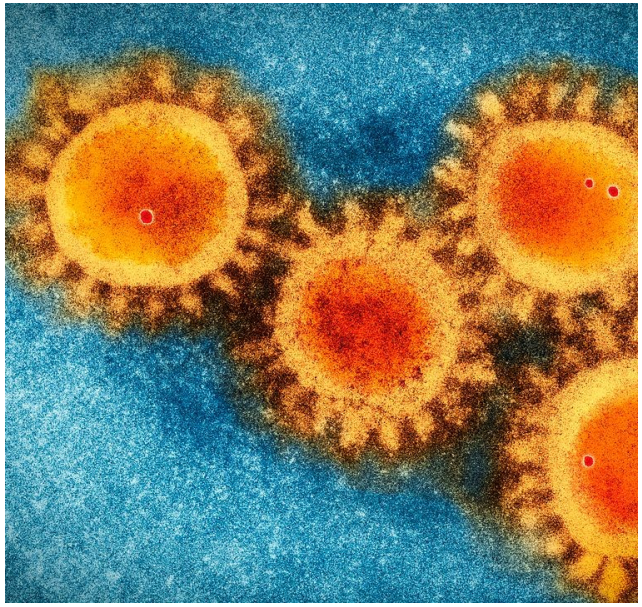
→ most MERS patients developed **severe respiratory illness** with symptoms of fever, cough and shortness of breath, severe complications followed, such as **pneumonia** and **kidney failure**, 72% of patients required arteficial ventilation, **35 % of patients with MERS have died** (ARDS + renal failure)

→ relatively high lethality and targeted anti-epidemic measures taken in the Middle East have prevented the global spread of infection, but we will certainly encounter local outbreaks of MERS in the future as well

→ MERS-CoV may have originated in **bats** later transmitted via **dromedaries (Arabian camels)** to human

Middle East Respiratory Syndrome





COVID-19 - Introduction

→ at the end of 2019, a novel coronavirus (2019-nCoV) was identified as the cause of a **cluster of pneumonia** cases in Wuhan, a city in the Hubei, province of China

→ not previously identified virus in humans, natural host suspected to be **bats**, as intermediate hosts were considered **Pangolins**, first cases in China linked with an **animal market**

→ novel coronavirus rapidly spread, resulting in an **epidemic throughout China**, followed by a **global pandemic** (WHO declared a global pandemic on **March 11, 2020**)

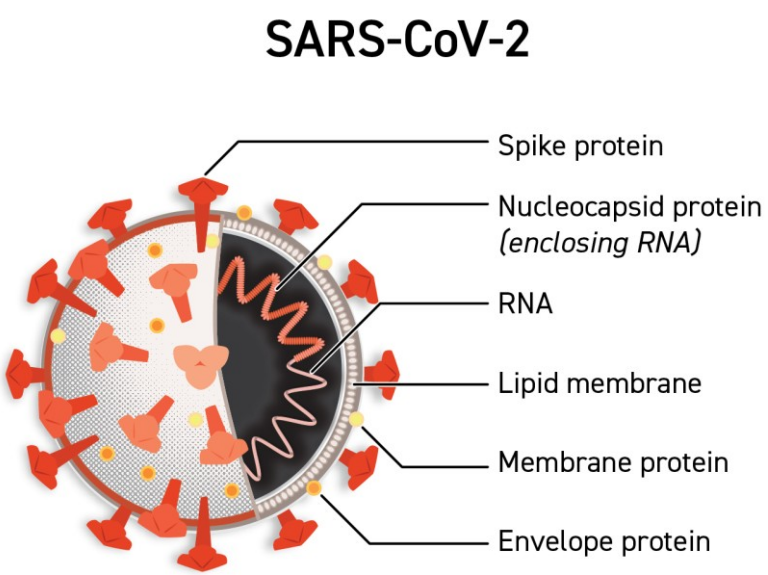
→ in February 2020 WHO designated the disease **COVID-19**, the virus that causes COVID-19 is designated **severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)**

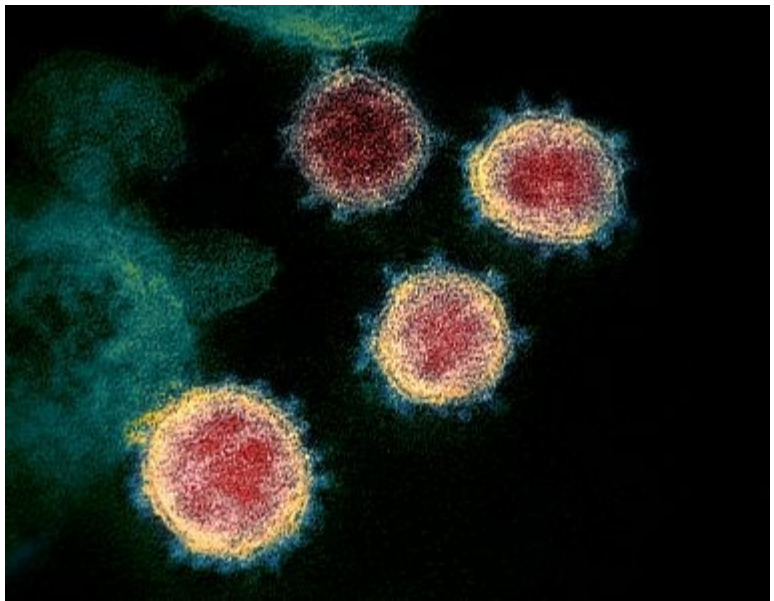
COVID-19 - Virology

→ SARS-CoV-2 is a **betacoronavirus** in the same subgenus (*Sarbecovirus*) as the severe acute respiratory syndrome (SARS) virus (as well as several bat coronaviruses)

→ the host receptor for SARS-CoV-2 cell entry is the same as for SARS-CoV-1, the **angiotensin-converting enzyme 2 (ACE2)**

→ the structural proteins of SARS-CoV-2 include membrane glycoprotein (M), envelope protein (E), nucleocapsid protein (N), and the **spike protein (S)**, the M protein of SARS-CoV-2 is 98,6% similar to the M protein of bat coronavirus, maintains 98,2% homology with pangolins coronavirus, and has 90% homology with the M protein of SARS-CoV-1; whereas, the similarity is only 38% with the M protein of MERS-CoV





COVID-19 - Virology

Variants of concern

B.1.1.7 Alpha	B.1.351 Beta	P.1 Gamma	B.1.617.2 Delta	B.1.1.529 Omicron
May 2020 UK	**August 2020** South Africa	**November 2020** Brazil	**October 2020** India	**November 2021** Multiple countries
Spreads more easily	Spreads more easily and some vaccines may be less effective against it	Spreads more easily and some vaccines may be less effective against it	Spreads more easily Symptoms may present differently May reduce vaccine efficacy Still protects against severe disease	Early studies show that it spreads more easily

Source: www.who.int/en/activities/tracking-SARS-CoV-2-variants/

wellcome

COVID-19 - Pathophysiology

→ SARS-CoV-2 **binds to ACE2** through the receptor-binding gene region of its **spike protein**, density of ACE2 receptors in each tissue **correlates with the severity** of the inflammation and tissue demage

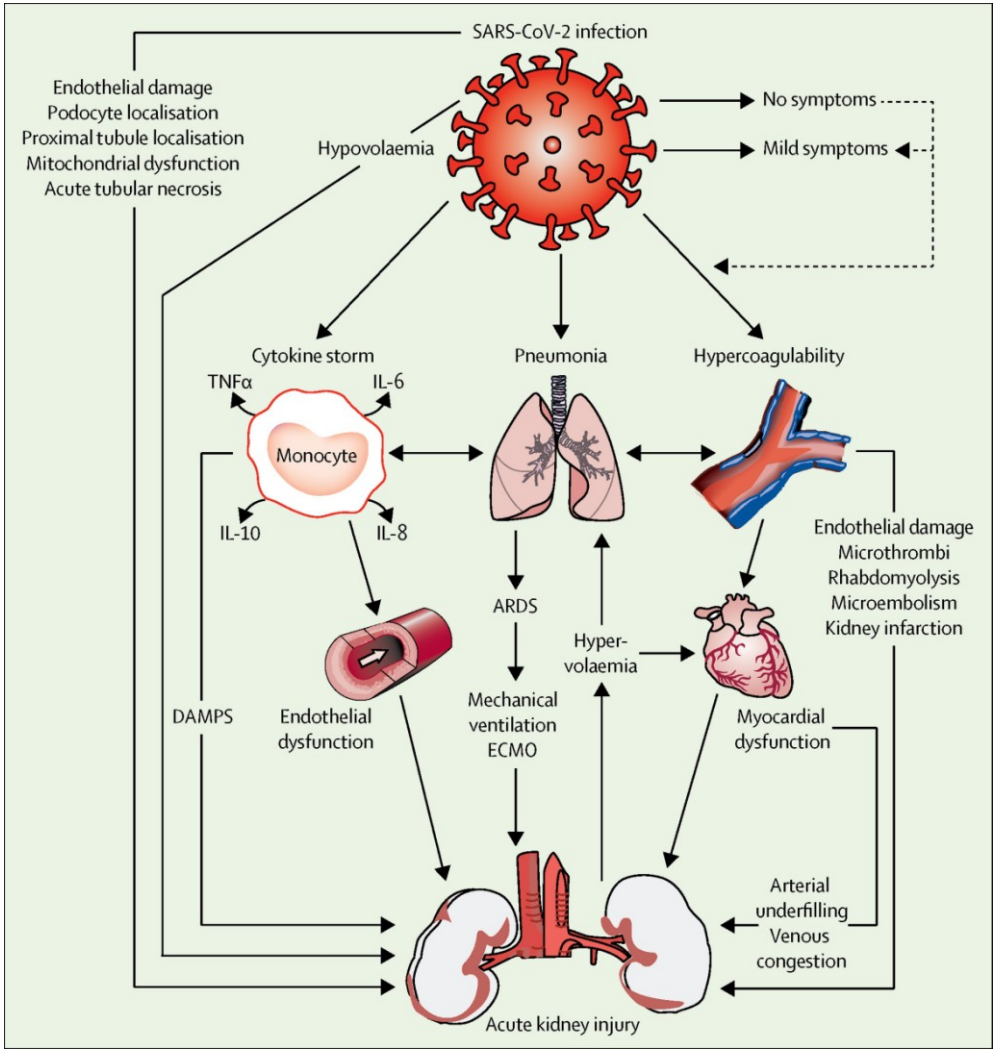
→ virus can affect the **upper respiratory tract** (sinuses, nose, throat) and the **lower respiratory tract** (windpipe and lungs), lungs are the organs most affected (ACE2 receptors are most abundant in type II alveolar cells)

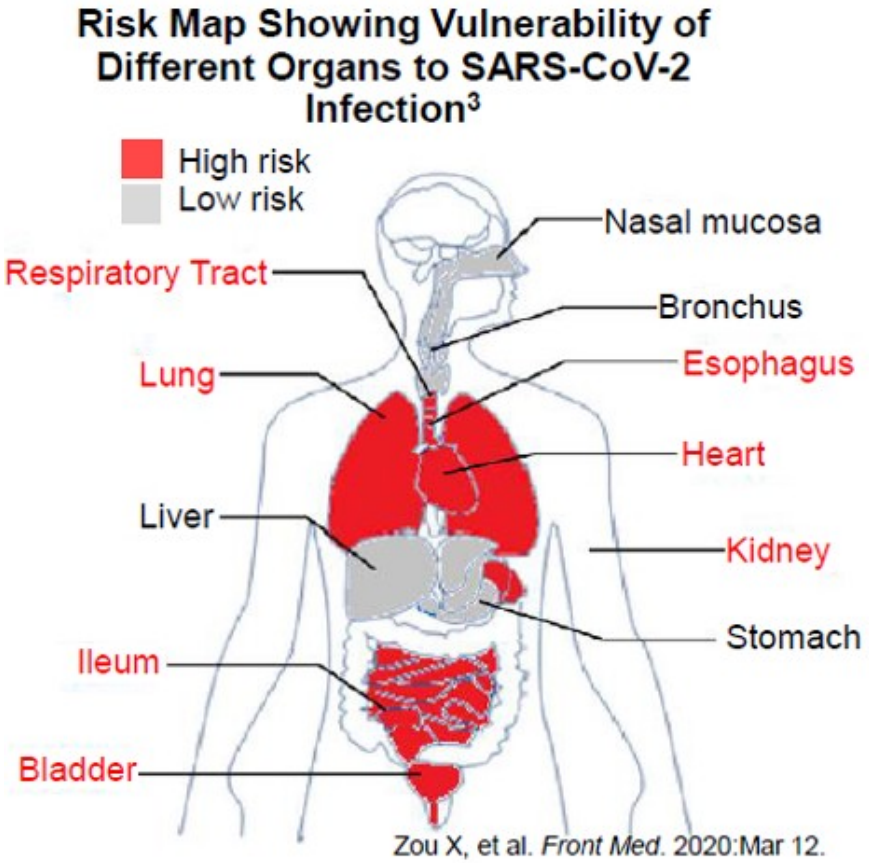
→ SARS-CoV-2 also affects **gastrointestinal organs** (ACE2 is abundantly expressed in the glandular cells of gastric, duodenal and rectal epithelium)

→ virus can cause **acute myocardial injury** (perimyocarditis in 12% of infected people admitted to the hospital in Wuhan), ACE2 receptors are highly expressed in the heart and in vascular endothelium

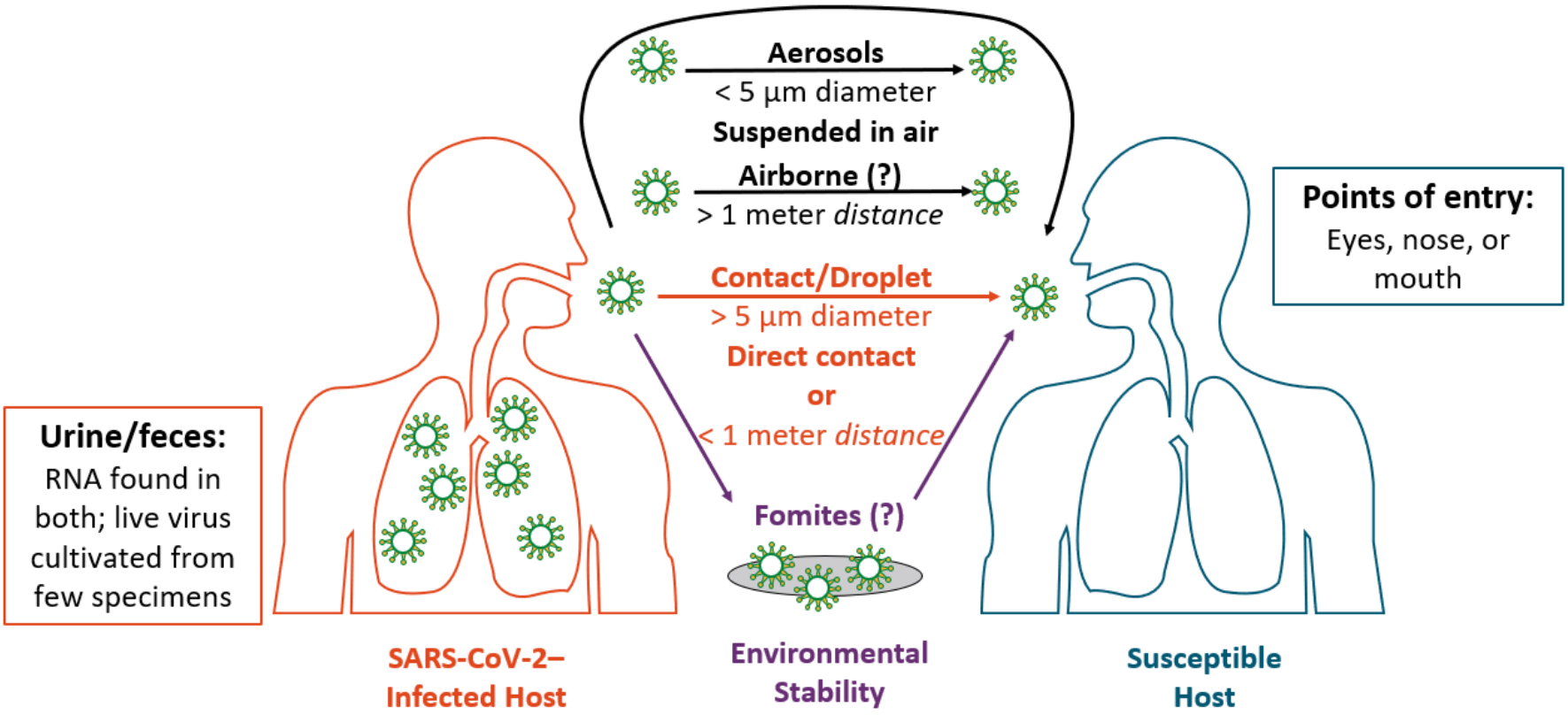
→ **blood vessel dysfunction** and **clot formation** (high D-dimer levels) are thought to play a significant role in mortality, incidences of clots leading to **pulmonary embolisms**, and **ischaemic events** within the brain have been noted as complications **leading to death**

COVID-19 - Pathophysiology





COVID-19 - Routes of Transmission



Galbadage. Front Public Health. 2020;8:163. WHO. Scientific Brief. July 9, 2020.

Slide credit: clinicaloptions.com

COVID-19 – Clinical Manifestations

→ symptoms of COVID-19 are variable, ranging from mild „flu-like“ symptoms to severe life-threatening illness with acute respiratory failure or MODS/MOF

The typical symptoms are:

→ **Fever or Subfebrile > 37.3 °C (83-99%)**

→ **Dry cough (59-82%)**

→ Fatigue, collapse states (44-70%)

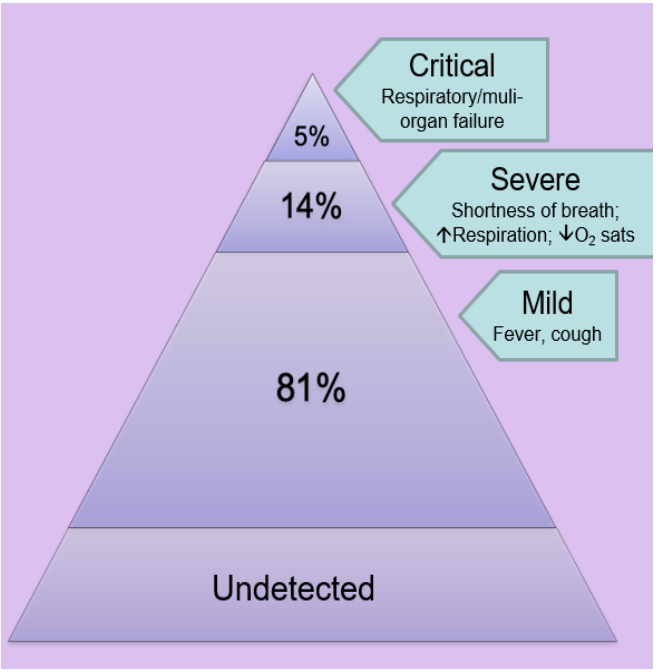
→ Anorexia (40-84%)

→ **Shortness of breath, dyspnoea (31-40%)**

→ Digestive symptoms **(diarrhea)** can be in up to 50%

→ Runny nose, sore throat, **loss of smell and taste**

Symptoms last 5 - 6 days



Severe illness (complications) starts usually after day 5-8:

→ **Interstitial bilateral pneumonia**

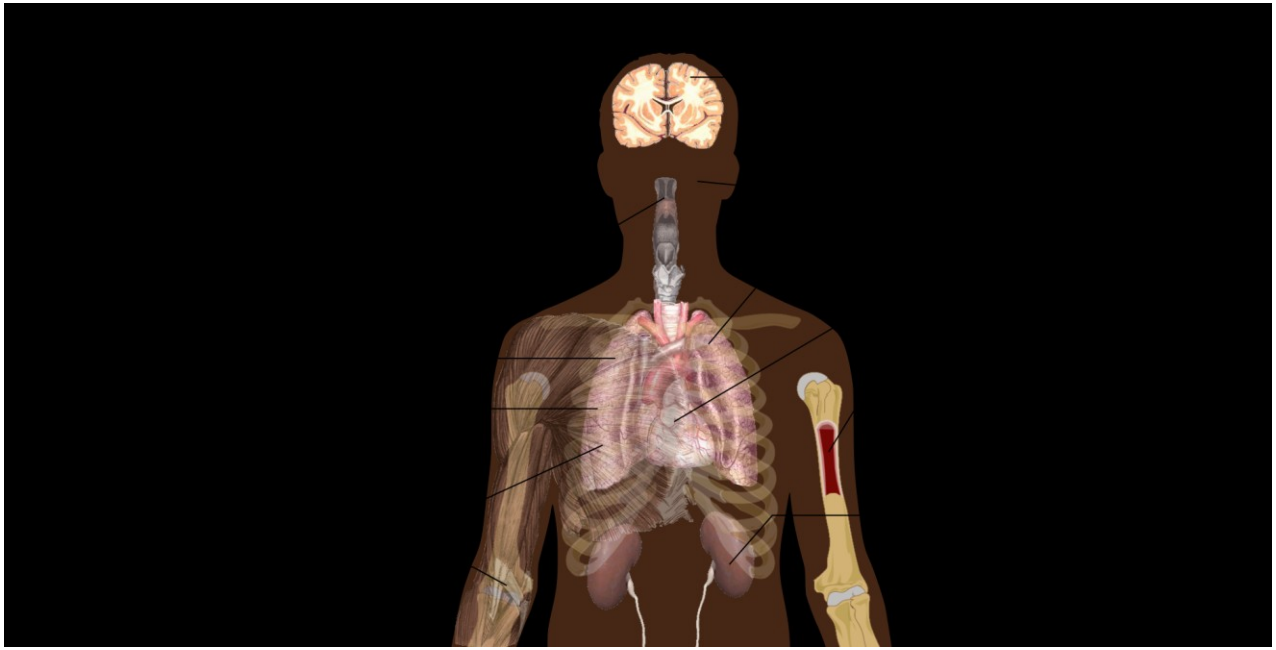
→ **Acute hypoxemic respiratory failure**

→ Perimyocarditis, acute heart failure

→ **Pulmonary embolism („in situ“)**

→ Kidney failure, disseminated intravascular coagulation, **secondary bacterial infection**...

COVID-19 – Clinical Manifestations



Product Line	Parameter	Lab abnormalities
Hematology	Neutrophile count	↑
	Lymphocyte count	↓
	Erythrocyte sedimentation rate	↑
Clinical Chemistry	C-reactive protein	↑
	Albumin	↓*
	Liver enzymes (GOT (AST), GPT (ALT), GGT, ALP, Bilirubin)	↑*
	Lactate dehydrogenase (LDH)	↑*
	Kidney parameters (Creatinine, Urea/BUN)	↑*
	Lactate	↑*
Cardiac Marker	CK-MB	↑*
	Myoglobin	↑*
	Troponin	↑*
Coagulation	D-dimer	↑*
	Prothrombin time (sec)	↑*

* in severe cases, mainly

[1] *Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7); Released by National Health Commission & State Administration of Traditional Chinese Medicine; March 3, 2020*

[2] *Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med 2020 Feb 24. doi: 10.1515/cclm-2020-0198*

COVID-19 – Risk Factors

Risk factors for more severe illness:

→ **Age 65 and older**

→ People who reside in nursing homes or long-term care facilities

People of all ages with underlying medical conditions:

→ **Chronic lung disease** (asthma bronchiale, COPD)

→ **Serious heart conditions**

→ Immunocompromise and **onkological patiens**

→ Severe obesity (BMI > 35)

→ **Diabetes mellitus**

→ Severe kidney disease

→ Chronic liver disease

Outcomes of COVID-19 patients in USA:

Adults > 65 represented:

→ 31% of COVID-19 cases

→ 45% of hospitalizations

→ 53% of ICU admissions

→ **80% of deaths**

COVID-19 – Risk Groups

LOW RISK

Contact studies indicate **children and young adults** do become infected, and can transmit infection. However, children rarely progress to serious illness

HIGH RISK

Risk of severe disease **increases with age** and in those with **underlying medical conditions** such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, cancer & obesity

https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19

COVID-19 – Diagnostics

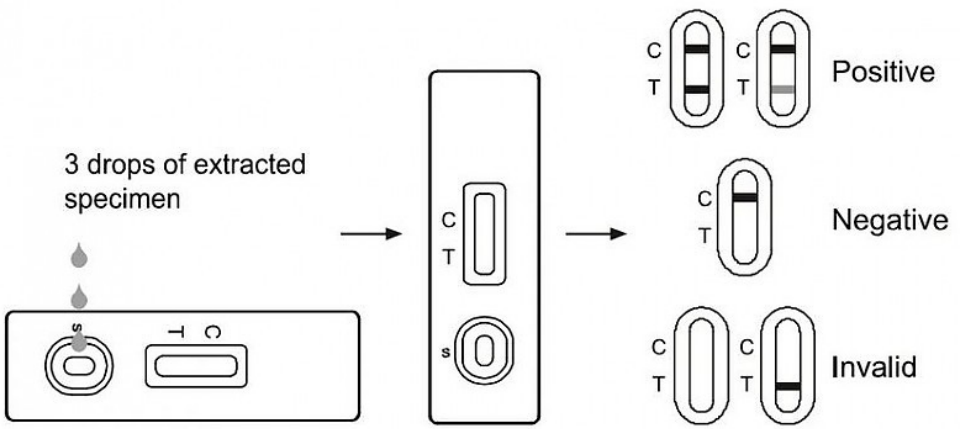
→ COVID-19 can be diagnosed on the basis of **typical clinical symptoms** (fever, dry cough, shortness of breath, diarrea, loss of smell and taste) and confirmed using **polymerase chain reaction (RT-PCR)** with the detection of viral in RNA in collected biological
→ test is typically done on respiratory samples obtained by a **nasopharyngeal swab**, however, a nasal swab, saliva or sputum sample may also be used

→ serologic tests detect **antibodies** (IgG, IgM, IgA) to SARS-CoV-2 in the blood and can help identify patients who **previously had COVID-19** as well as patients with current infection who have had symptoms **for three to four weeks**

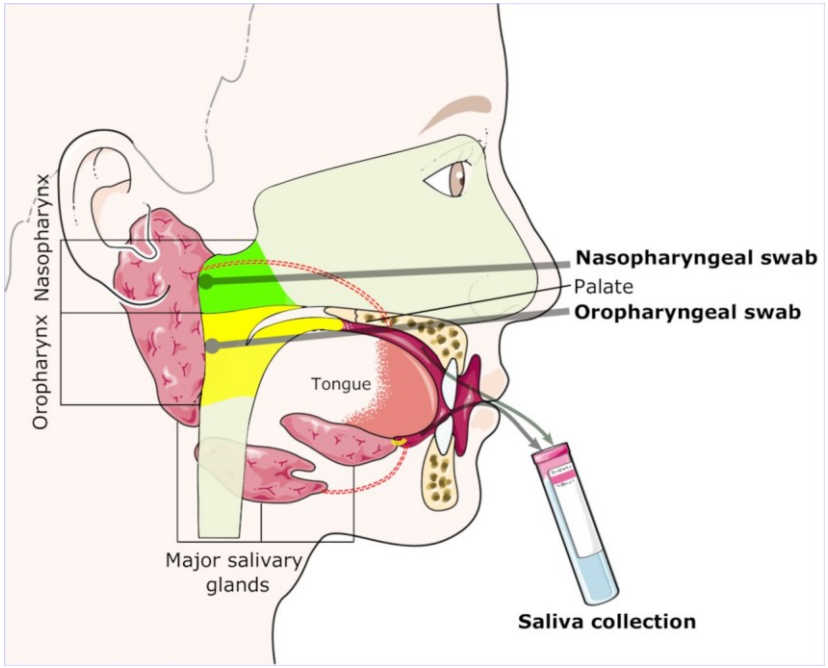
→ **antigen detection tests** detect viral antigens (nucleocapsid or spike protein), their advantage is speed and low price (can be performed **at the point of care**), the disadvantage is **lower sensitivity**
→ negative antigen test result (in a symptomatic patient) should be always **confirmed by PCR test**

COVID-19 – Diagnostics

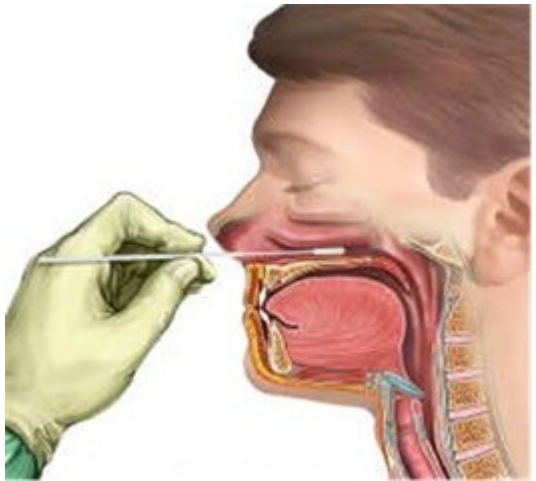
Test category	Primary clinical use	Specimen type	Performance characteristics	Comments
NAATs (including RT-PCR)	Diagnosis of current infection	Respiratory tract specimens	▪ High analytic sensitivity and specificity in ideal settings. ▪ Clinical performance depends on the type and quality of the specimen and the duration of illness at the time of testing. ▪ Reported false-negative rate ranges from <5 to 40%, depending on the test used. ¶	▪ Time to perform the test ranges from 15 minutes to 8 hours. Δ ▪ Turnaround time is influenced by the test used and laboratory workflow. ▪ Some assays allow home collection of specimens that are mailed in.
Serology (antibody detection)	Diagnosis of prior infection (or infection of at least 3 to 4 weeks' duration)	Blood	▪ Sensitivity and specificity are highly variable. ▪ Detectable antibodies generally take several days to weeks to develop; IgG usually develops by 14 days after onset of symptoms. ▪ Cross-reactivity with other coronaviruses has been reported. ▪ Individual results should be interpreted with caution in settings of low seroprevalence; serologic tests that have high specificity still have a low positive predictive value.	▪ Time to perform the test ranges from 15 minutes to 2 hours. ▪ Turnaround time is influenced by the test used and laboratory workflow. ▪ It remains uncertain whether a positive antibody test indicates immunity against future infection.
Antigen tests	Diagnosis of current infection	Nasopharyngeal or nasal swabs	▪ Data are limited. ▪ Antigen tests are generally less sensitive than nucleic acid tests.	▪ Time to perform the test is <1 hour.



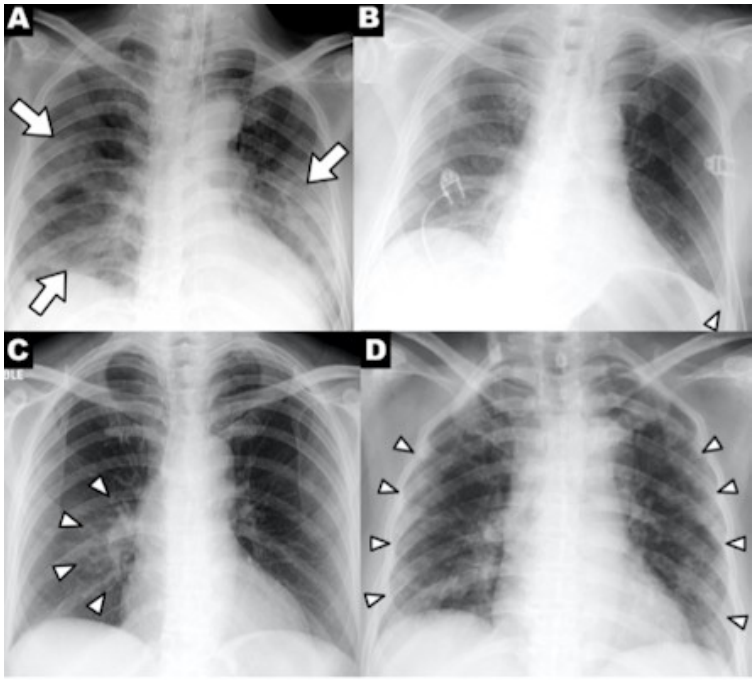
COVID-19 – Diagnostics

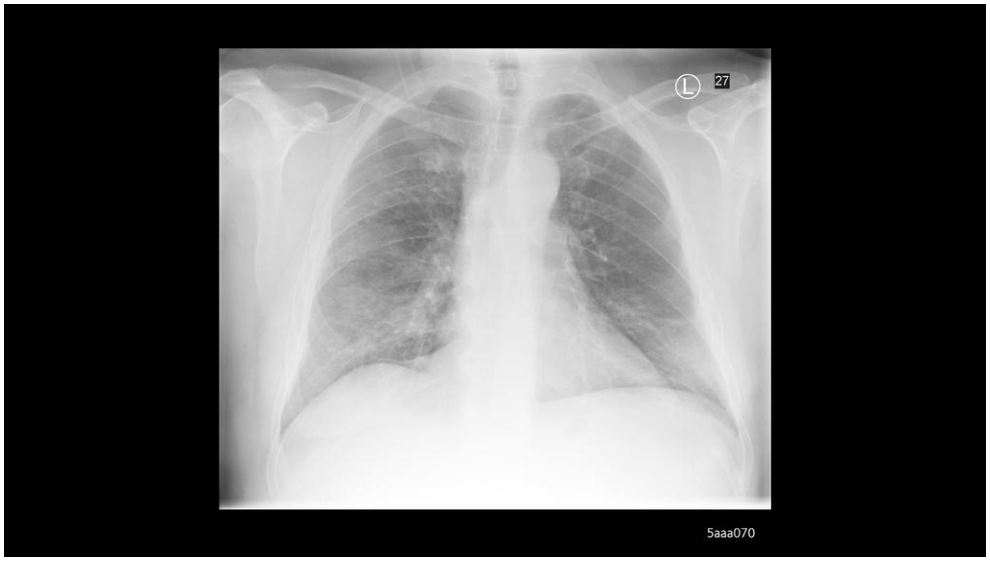


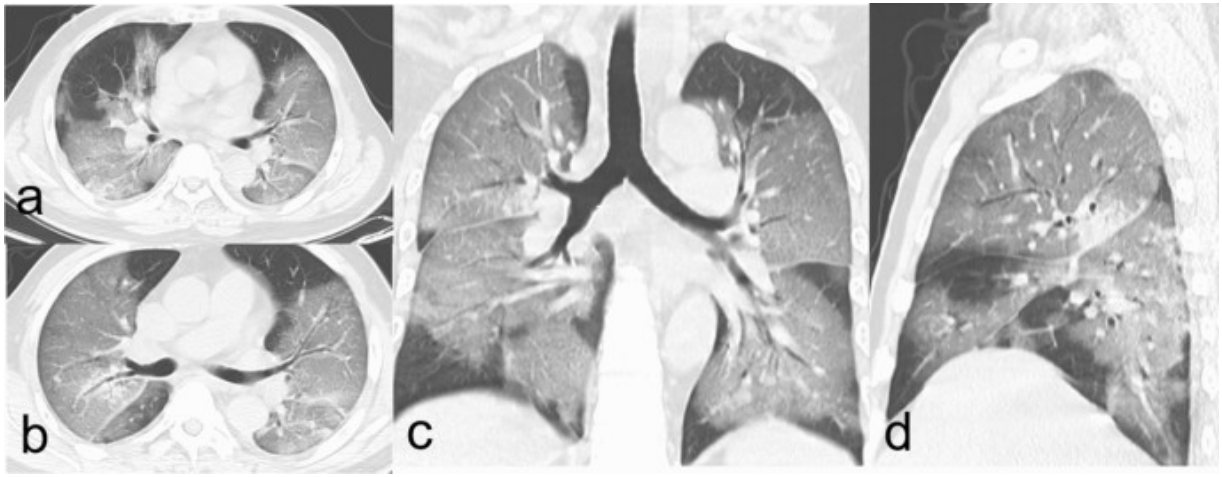
Is crucial to know how to collect the sample (nasophyryngeal swab) properly!

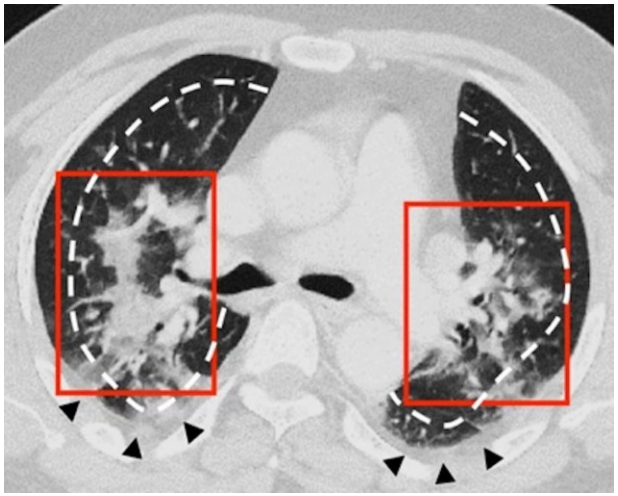


COVID-19 – Imaging Modalities









COVID-19 – Treatment Options

→ the management of COVID-19 includes especially **supportive and symptomatic care**, the possibilities of **targeted therapy are limited**, they are still in the research stage

→ treatment in mild forms of COVID-19 takes place **in most cases in home isolation**, in case of development of dyspnea or other complications, hospitalization is necessary

Non-specific therapy includes:

→ close **monitoring** for symptomatic patients with risk factors for severe disease (blood pressure, pulse, blood oxygen saturation level, GCS, qSOFA…)

→ empiric **antibiotics** (ceftriaxone, cotrimoxazole, meropenem) are administered if bacterial pneumonia strongly suspected (CRP > 100, positive prokalcitonin)

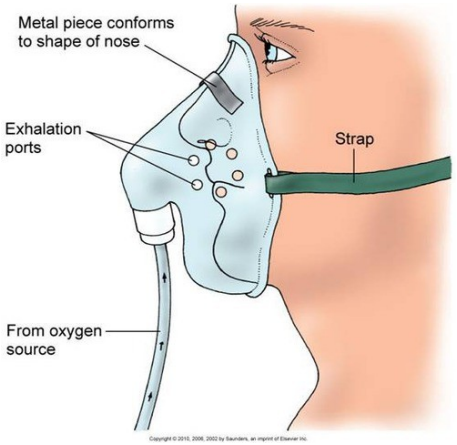
→ symptomatic care (**antipyretics**, fluid therapy, NSAIDs, **antitussives** and mucolytics)

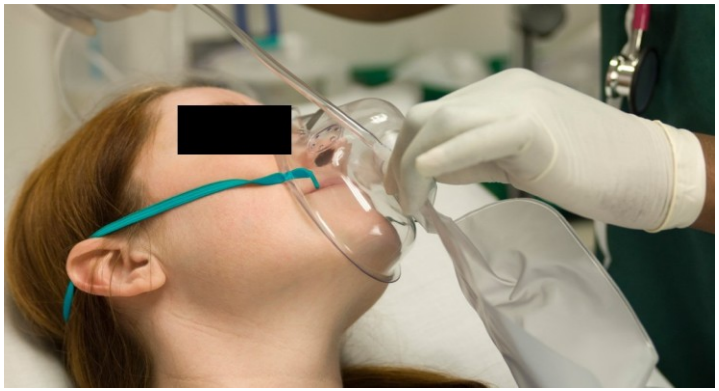
→ supportive care (**vitamins**, probiotics, nutrition, rehabilitation, **prone position**)

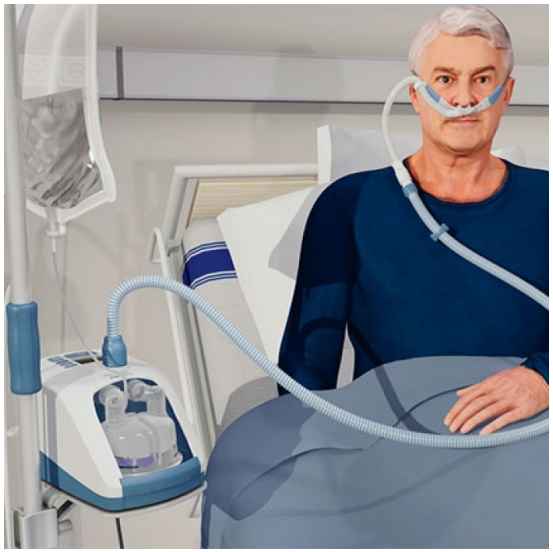
→ prophylaxis of thromboembolic disease **(LMWH)** in all hospitalized patients **+ ASA**

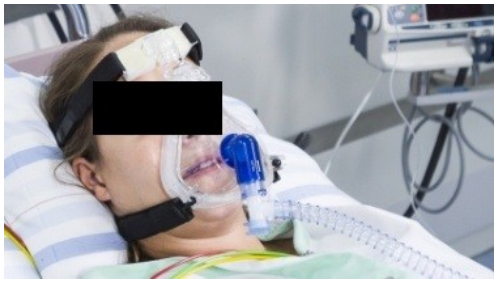
→ **oxygen support**: low-dose oxygen (nasal cannula, simple face mask, **non-rebreather masks**), **high-flow nasal oxygen therapy** (HFNO, Airvo), non-invasive ventilation, orotracheal intubation and artificial lung ventilation, ECMO

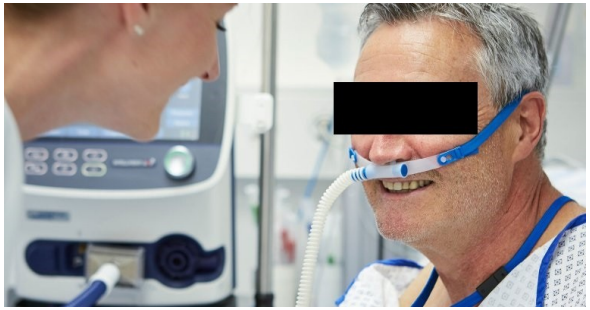
COVID-19 – Oxygen Therapy

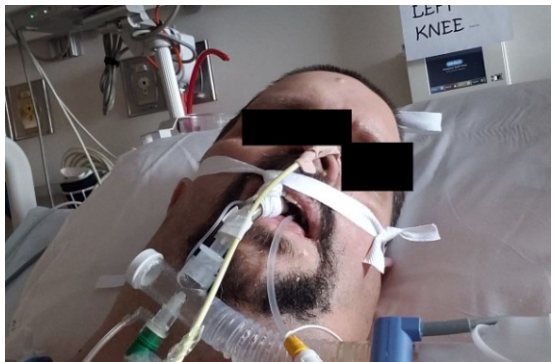












COVID-19 – Specific Therapy

Glucocorticoids (dexamethasone)

→ data from randomized trials support the role of glucocorticoids for severe COVID-19, in a meta-analysis of seven trials that included 1703 critically ill patients **glucocorticoids reduced 28-day mortality** compared with standard care or placebo **(32 % versus 40 %)** and were not associated with an increased risk of severe adverse events

Proposed mechanism of action:

→ the sickest patients with COVID-19 suffer a **hyperinflammatory state** (cytokine storm)

→ immune suppression should help such patients, by contrast, immune suppression during the early phase of the viral infection might allow increased viral replication and aggravate the disease!

→ **inhaled glucocorticoids** – in trials evaluating inhaled glucocorticoids, there was some benefit in the treatment of mild, early, COVID-19, although no mortality reduction was demonstrated

→ dexamethasone (or e.g. methylprednisolone) is recommended for severely ill patients with COVID-19 who are on supplemental oxygen or ventilatory support

COVID-19 – Specific Therapy

Remdesivir (GS-5734, Veklury®)

→ a novel nucleotide analogue**, inhibitor of the viral RNA-dependent RNA polymerase** with in vitro inhibitory activity against SARS-CoV-2 (and SARS-CoV-1, MERS-CoV...)

→ remdesivir in ACTT-1 study (2020) resulted in a **faster time to recovery**, defined as discharge from the hospital or continued hospitalization without need for supplemental oxygen or ongoing medical care **(median 10 versus 15 days),** remdesivir reduced time to recovery whether patients were randomized within or after 10 days of symptom onset, however, in subgroup analysis, the reduced time to recovery was only statistically significant among patients who were on **low-flow oxygen at baseline**

→ in the EU, remdesivir is indicated for the treatment of COVID-19 in adults and adolescents with intersticial pneumonia requiring supplemental oxygenotherapy, we prioritize remdesivir for those requiring low-flow oxygen because it may also reduce mortality in this population

→ suggested adult dose is 200 mg intravenously on day 1 followed by 100 mg daily for 5 days total

COVID-19 – Specific Therapy

Monoclonal antibodies

1) Monoclonal antibodies anti-SARS CoV-2:

→ developed to **neutralize SARS-CoV-2 by targeting the SARS-CoV-2 proteins (e.g. spike protein)** and preventing viral cell entry

→ bamlanivimab/etesevimab (Eli Lilly), **casirivimab/imdevimab** (Regeneron), sotrovimab

→ therapy and also postexposure prophylaxis in patients who are at high risk for progression to severe COVID-19

2) Inflammatory pathways inhibitors:

→ elevated inflammatory markers and elevated pro-inflammatory cytokines (e.g. IL-6) are associated with critical COVID-19 → **blocking the inflammatory pathway** has been hypothesized to prevent disease progression **(cytokine storm)**

→ these include the IL-6 receptor blockers **tocilizumab** and sarilumab, the direct IL-6 inhibitor siltuximab, JAK (Janus kinase 1 and 2) inhibitor **baricitinib**

Approaches that target the virus itself are more likely to work early in the course of infection, whereas approaches that modulate the immune response may have more impact later in the disease course.

COVID-19 – Specific Therapy

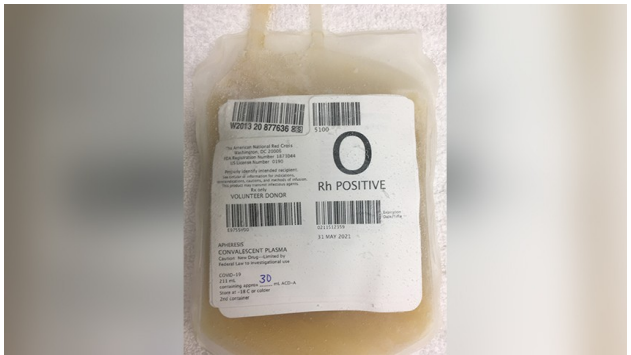
Convalescent plasma

→ plasma obtained from individuals who have recovered from COVID-19 can provide **passive antibody-based immunity**, neutralizing antibodies are thought to be the main active component

→ plasma that contains high neutralizing antibody titers is hypothesized to have clinical benefit when **given early in the course of disease** (first 3 - 5 days), and it may be of particular interest for individuals with deficits in antibody production

Favipiravir

→ **RNA polymerase inhibitor** that is available in Asian countries for treatment of influenza, is being evaluated in clinical trials for treatment of COVID-19 in the United States and elsewhere, favipiravir **may hasten SARS-CoV-2 RNA clearance**, although data are limited



COVID-19 – Specific Therapy

Molnupiravir (Lagevrio)

→ potent ribonucleoside analog that inhibits the replication of SARS-CoV-2

→ exerts its antiviral action through introduction of **copying errors** during viral RNA replication

→ I: treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19; CI: pregnancy, breastfeeding, people under 18

Tixagevimab/cilgavimab (Evusheld)

→ long-acting monoclonal antibody combination

→ I: pre-exposure prophylaxis of COVID-19 in adults and adolescents with moderate to severe immune compromise who may not mount an adequate immune response to COVID-19 vaccination

→ duration of protection is estimated to be **at least 6 months**

Nirmatrelvir/ritonavir (Paxlovid)

→ potent orally active 3C-like protease inhibitor

→ a number of drug interactions (ritonavir induces CYP1A2 and inhibits CYP 3A4 and 2D6)

COVID-19 – Prevention and Control

→ in locations where community transmission is **widespread**, preventive strategies for all individuals in a health care setting are warranted **to reduce potential exposures**!

Personal preventive measures:

→ **diligent hand washing**, particularly after touching surfaces in public, use of hand sanitizer that contains at least 60% alcohol

→ social/physical **distancing** (CDC recommends a minimum distance of **two meters**)

→ respiratory hygiene (covering the cough or sneeze)

→ avoiding touching the face (in particular eyes, nose, and mouth)

→ **cleaning and disinfecting objects** and surfaces that are frequently touched

→ adequate **ventilation of indoor spaces**

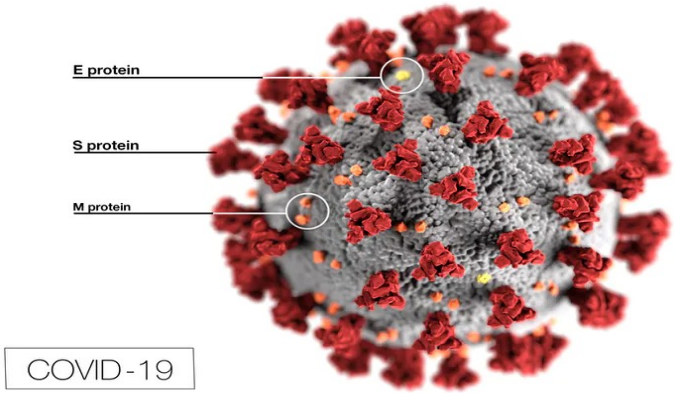
→ optimize of health of individuals (quit smoking, minimize alcohol, healthy diet, get adequate sleep, regular physical activity...)

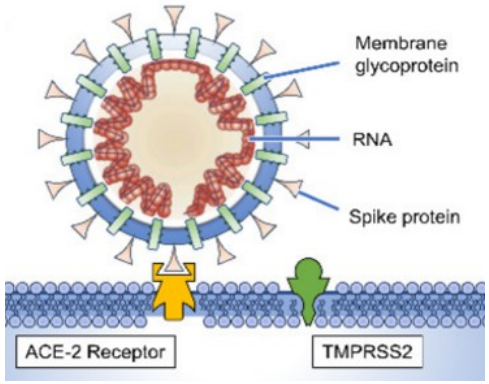
Wearing masks in the community:

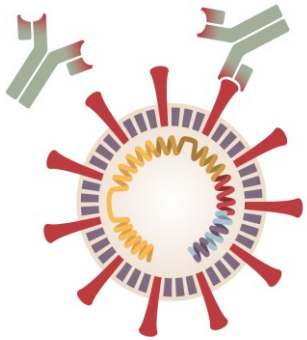
- a surgical mask or **respirators (FFP2)**
- **in public spaces, inside buildings, in public transport** or when around individuals outside of their household

COVID-19 – Prevention and Control

COVID-19 – Vaccines







Passive immunization - administration of **ready-made virus neutralizing antibodies** (immunoglobulins) to the human body

COVID-19 – Vaccines

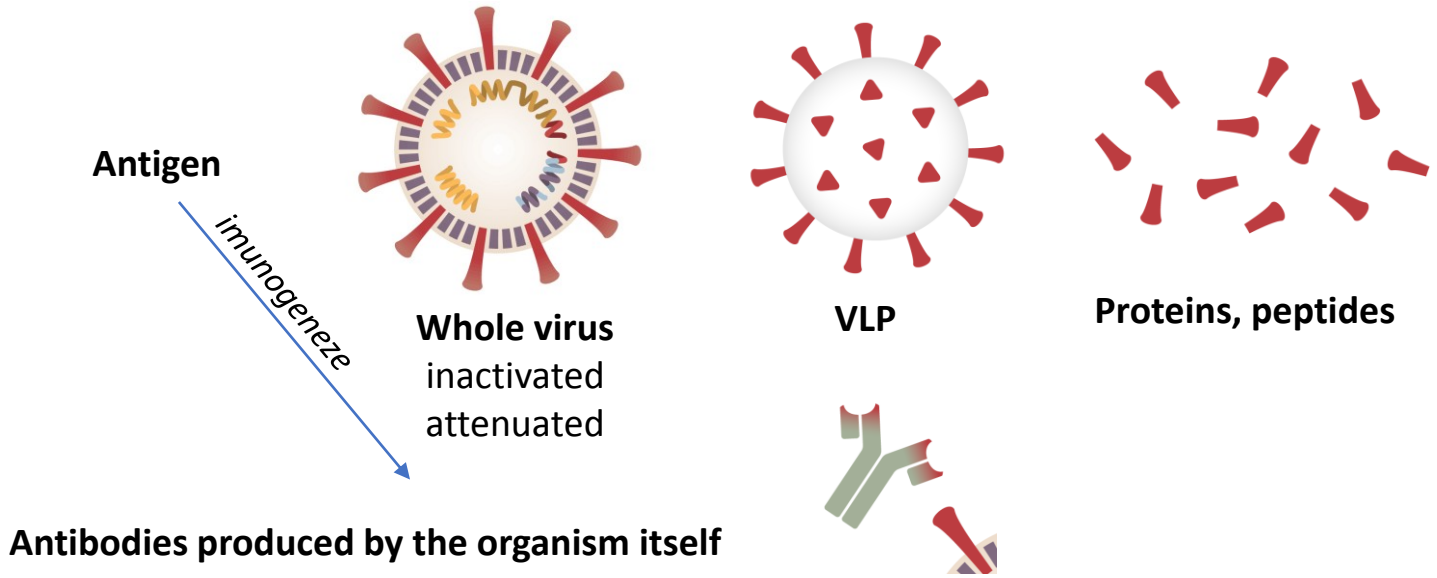
Passive immunization - administration of **ready-made virus neutralizing antibodies** (immunoglobulins) to the human body

Lilly

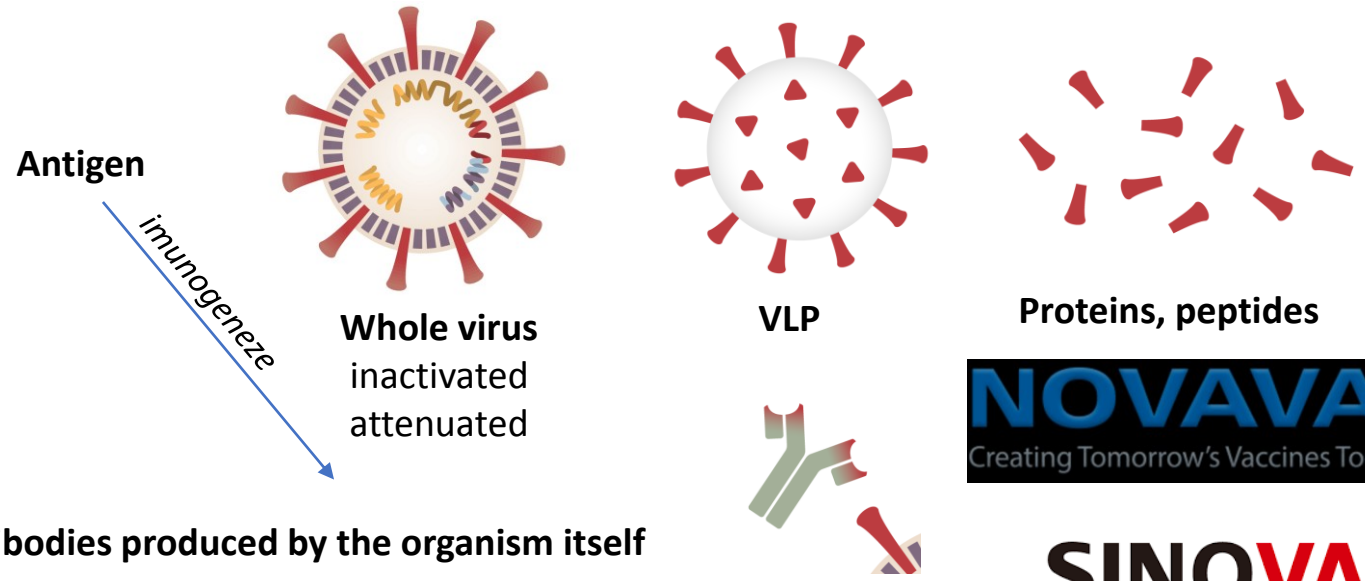
REGENERON
SCIENCE TO MEDICINE®

+ convalescent plasma

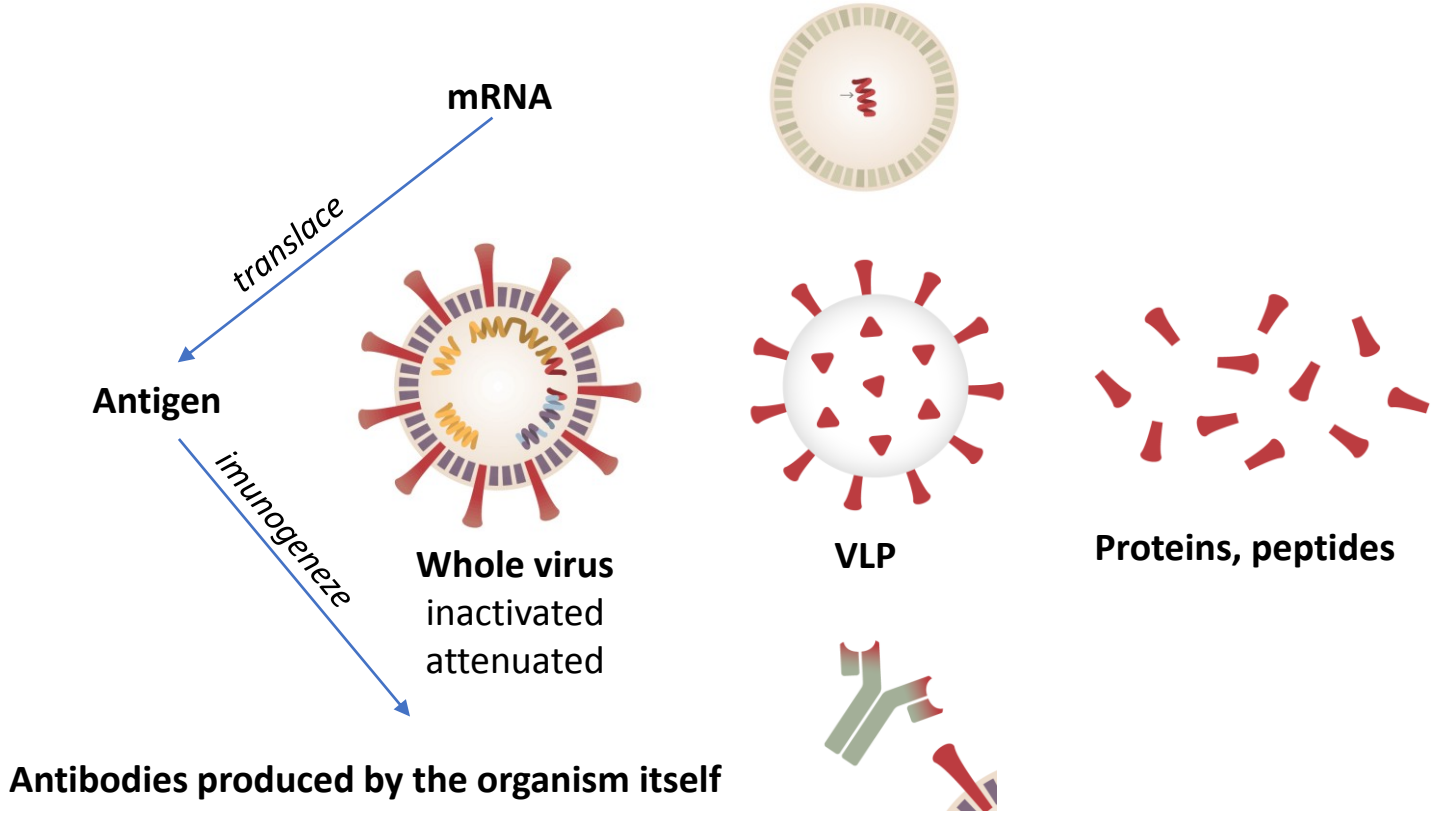
COVID-19 – Vaccines



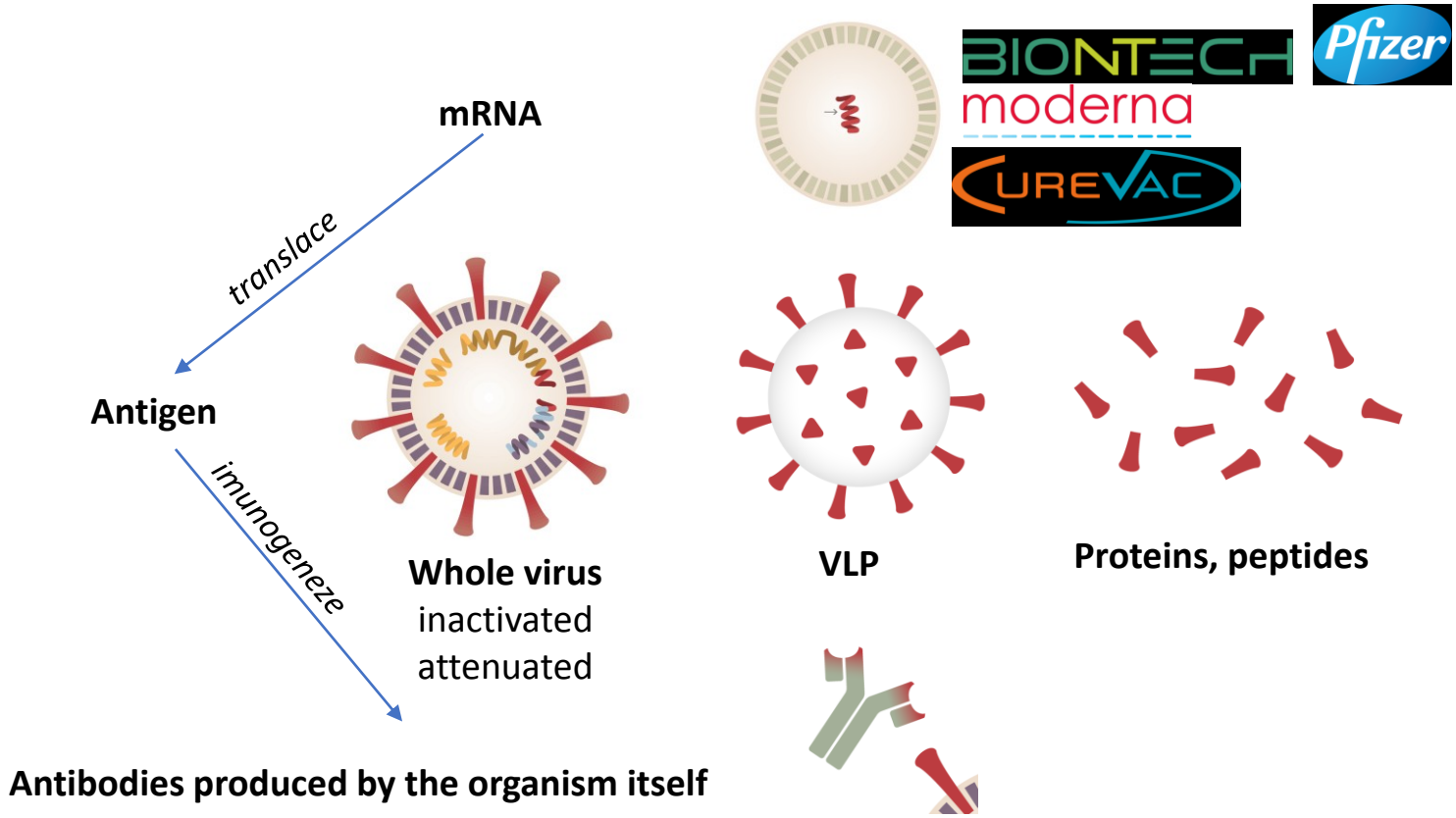
COVID-19 – Vaccines



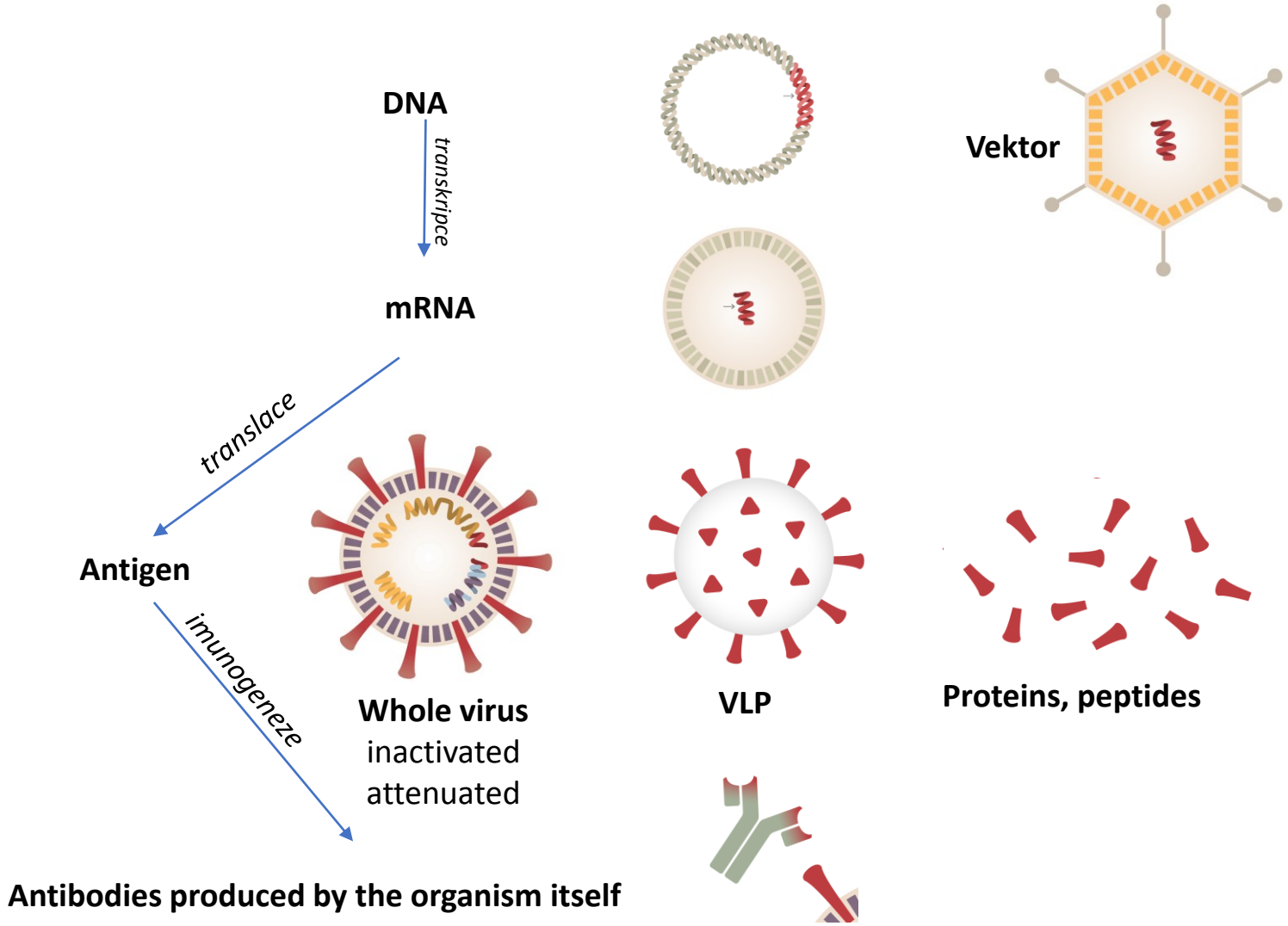
COVID-19 – Vaccines



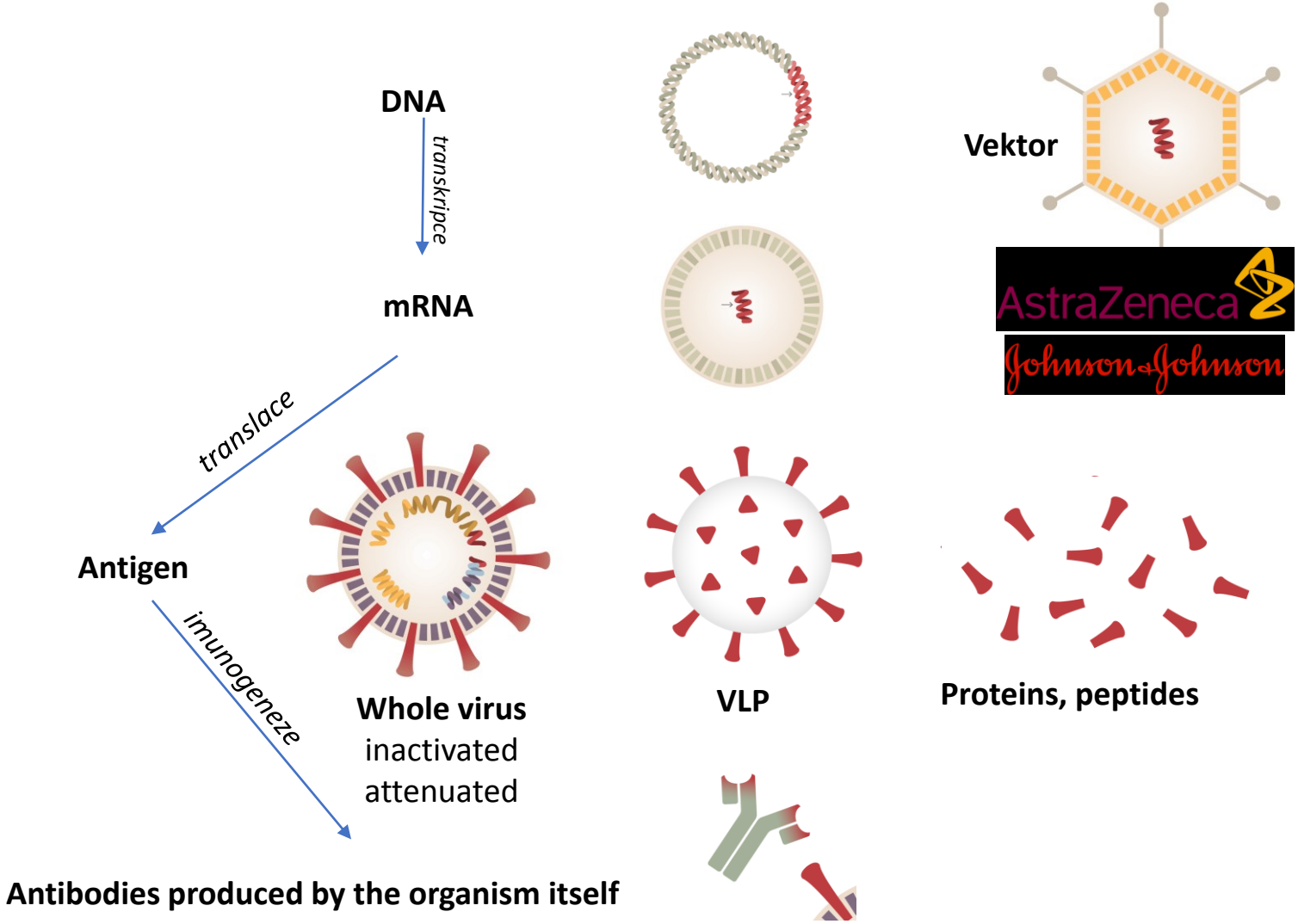
COVID-19 – Vaccines



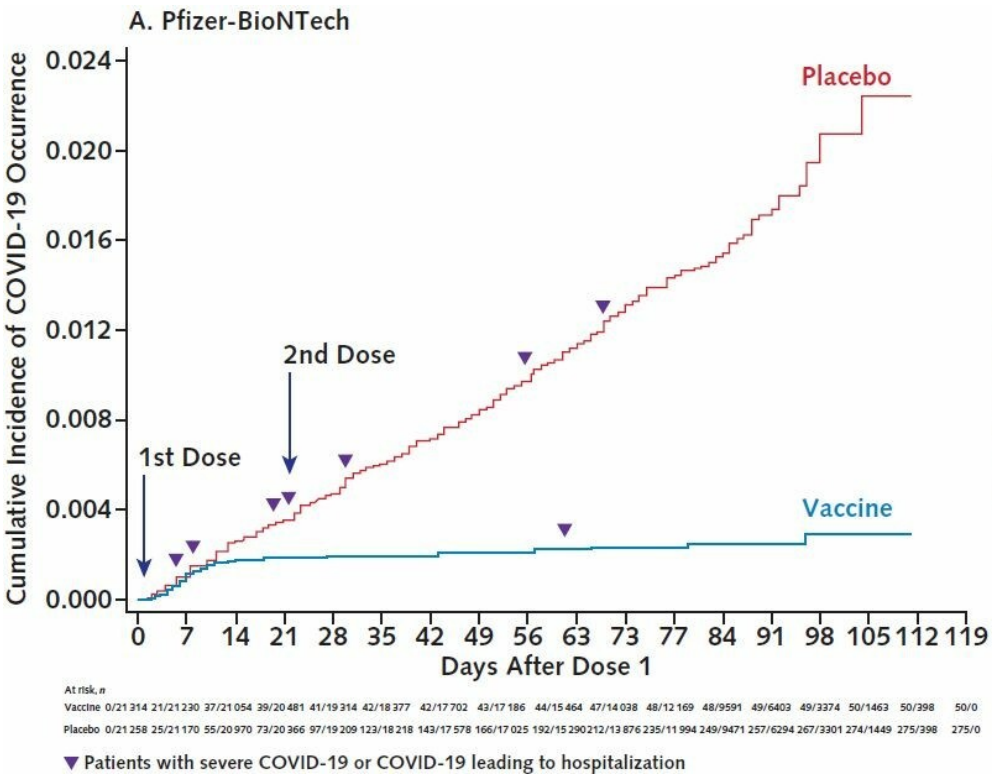
COVID-19 – Vaccines

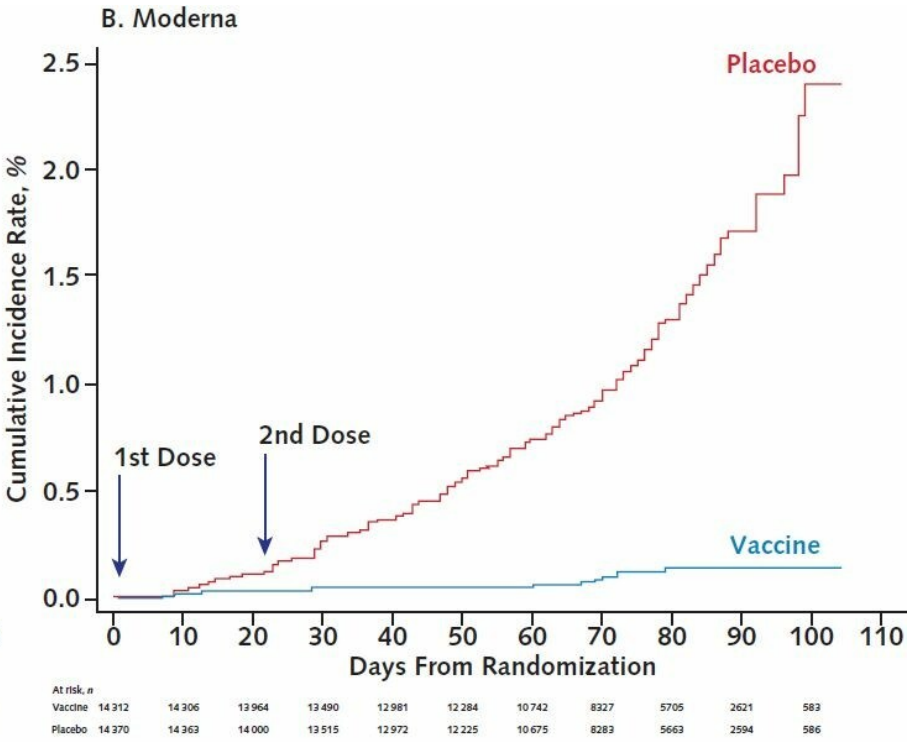


COVID-19 – Vaccines



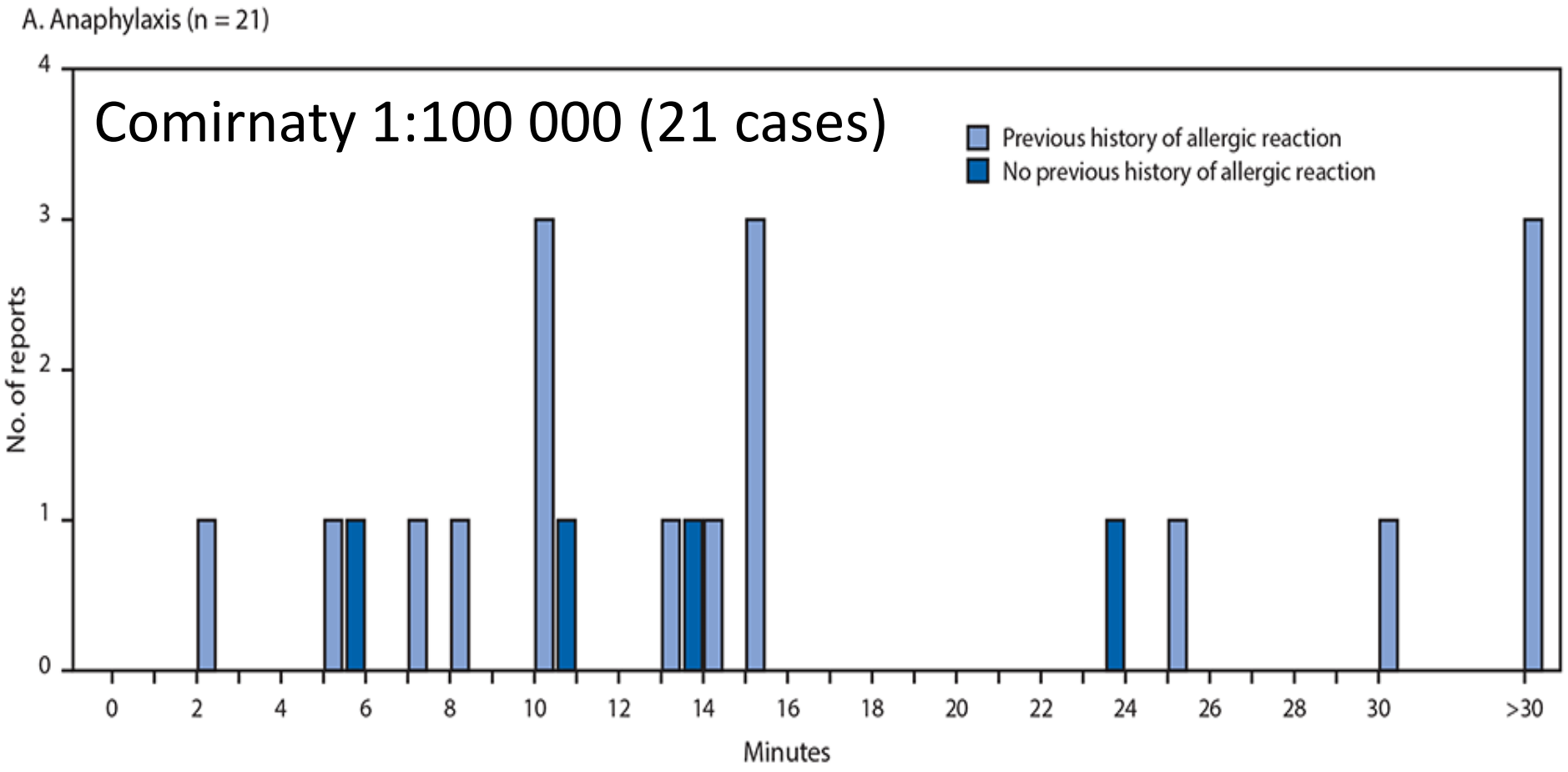
COVID-19 – Vaccines





Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. NEJM, 2020; 383:2603-2615.
DOI: 10.1056/NEJMoa2034577

COVID-19 – Vaccines



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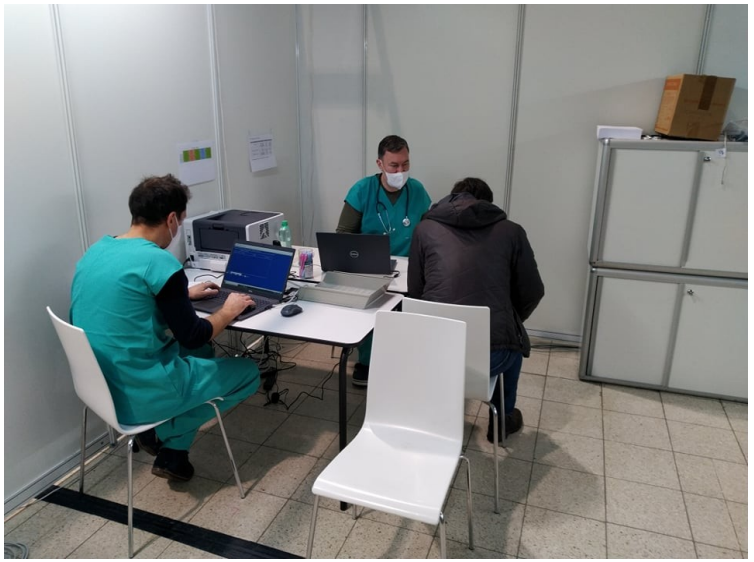

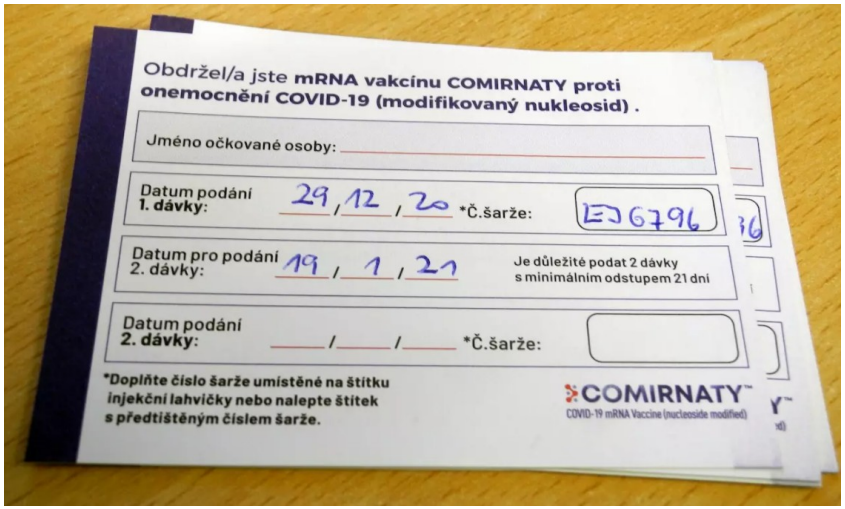

Obdržel/a jste **mRNA vakcínu COMIRNATY proti onemocnění COVID-19 (modifikovaný nukleosid) .**

Jméno očkované osoby: _____

Datum podání **1. dávky:** 29 / 12 / 20 *Č.šarže: EJ6796

Datum pro podání **2. dávky:** 19 / 1 / 21 Je důležité podat 2 dávky s minimálním odstupem 21 dní

Datum podání **2. dávky:** ___ / ___ / ___ *Č.šarže:

*Doplňte číslo šarže umístěné na štítku injekční lahvičky nebo nalepte štítek s předtištěným číslem šarže.

COMIRNATY™ COVID-19 mRNA Vaccine (nucleoside modified)

Certifikát o provedené vakcinaci
Certificate of vaccination

Jméno a příjmení (Name and Surname)

Kočka Testovací

Číslo pojištěnce (Health insurance number)	Číslo občanského průkazu (ID No.)	Číslo pasu (Passport No.)
CZ1252156		

Datum narození / Date of birth (yyyy-mm-dd): 1910-01-01

Původce, proti kterému byla vakcinace provedena: (Agent vaccinated against)	SARS-CoV-2 (ICD 11 XN109, SNOMED CT 840533007)			
Typ očkovací látky: Vaccine:	mRNA vakcína proti onemocnění COVID-19 COVID-19 mRNA Vaccine, Severe acute respiratory syndrome coronavirus 2 mRNA only vaccine product(SNOMED CT 1119349007)			
Název produktu: (Name of medicinal product)	Comirnaty			
Držitel rozhodnutí o registraci: (Marketing Authorization Holder)	BioNTech Manufacturing GmbH			
Země vakcinace: (Country of vaccination)	CZ	Kód vakcinančního centra: (Vaccination center code)		IČ 23833 PČZ
Vakcinace ukončena: Vaccination schedule completed:	Ano Yes	Dávka/celkový počet dávek (Number in a series of vaccination/doses)		2/2
Šarže (Batch number)	Dávka(dose) 1/2	CZ33333	Dávka(dose) 2/2	CZ33333
Vydavatel certifikátu: Certificate issued by:	Ministerstvo zdravotnictví České republiky Ministry of Health of the Czech Republic			
Datum vakcinace: (Date of vaccination YYYY-MM-DD)	2021-01-18	Datum vystavení certifikátu: (Certificate issued YYYY-MM-DD)		2021-01-18

Certifikát vystavil (Signature)

Identifikátor certifikátu (Unique identifier of the certificate):

EU Digital COVID Certificate

Certifikát EU COVID-19

CZ

Place QR code here
Minimum size 50 - 60 mm

Surname(s) and forename(s)
Příjmení a jméno
První František

Date of birth
Datum narození
1990-01-01

Unique certificate identifier
Unikátní identifikátor certifikátu
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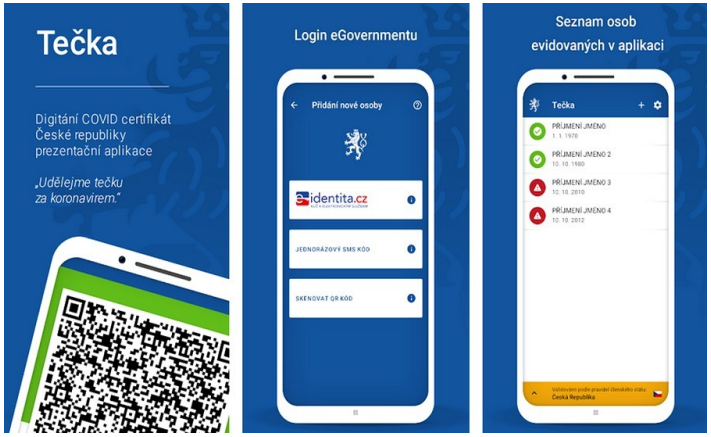

stebel.roman@fnbrno.cz

Resources

→ https://www.uptodate.com/contents/coronavirus-disease-2019
→ https://clinicaloptions.com/c19
→ https://www.cdc.gov/coronavirus/2019-ncov/index.html
→ https://www.who.int/emergencies/diseases/novel-coronavirus-2019

Beigel JH, Tomashek KM, Dodd LE, *et al*. Remdesivir for the Treatment of Covid-19 — Final Report. *N Engl J Med*. 2020;383(19):1813-1826. doi:10.1056/NEJMoa2007764

Hemmati F, Saedi S, Hemmati-Dinarvand M, Zarei M, Seghatoleslam A. Mysterious Virus: A Review on Behavior and Treatment Approaches of the Novel Coronavirus, 2019-nCoV. *Archives of Medical Research*. 2020;51(5):375-383. doi:10.1016/j.arcmed.2020.04.022

Qin Y-Y, Zhou Y-H, Lu Y-Q, et al. Effectiveness of glucocorticoid therapy in patients with severe coronavirus disease 2019: protocol of a randomized controlled trial. *Chinese Medical Journal*. 2020;133(9):1080-1086. doi:10.1097/CM9.0000000000000791

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