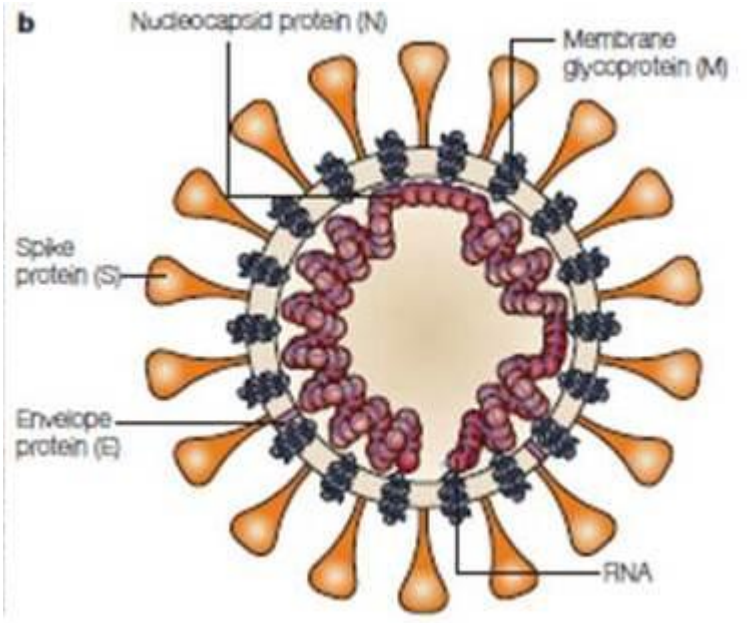
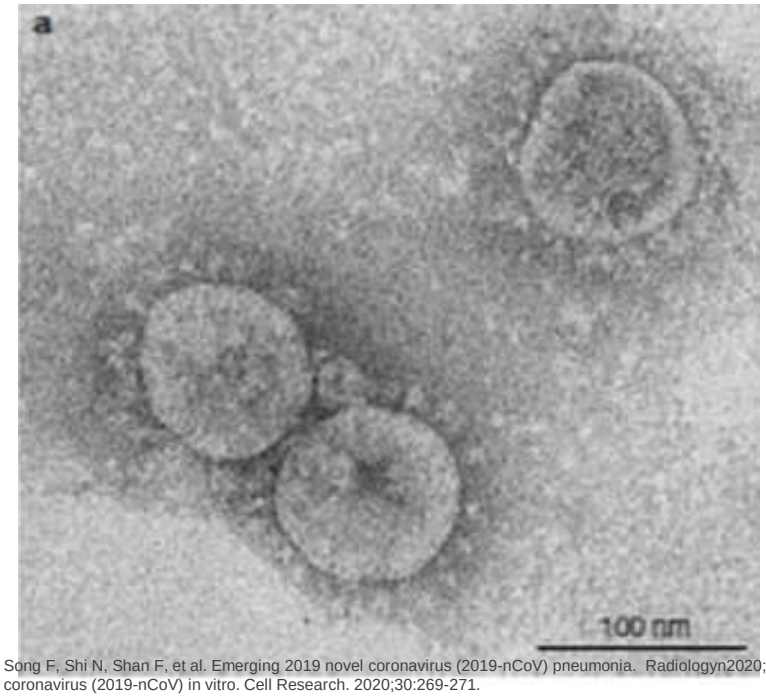
# SARS, MERS, COVID-19

Svatava Snopková, 4/2020

# The family Coronaviruses




Constitute the subfamily ***Orthocoronavirinae***

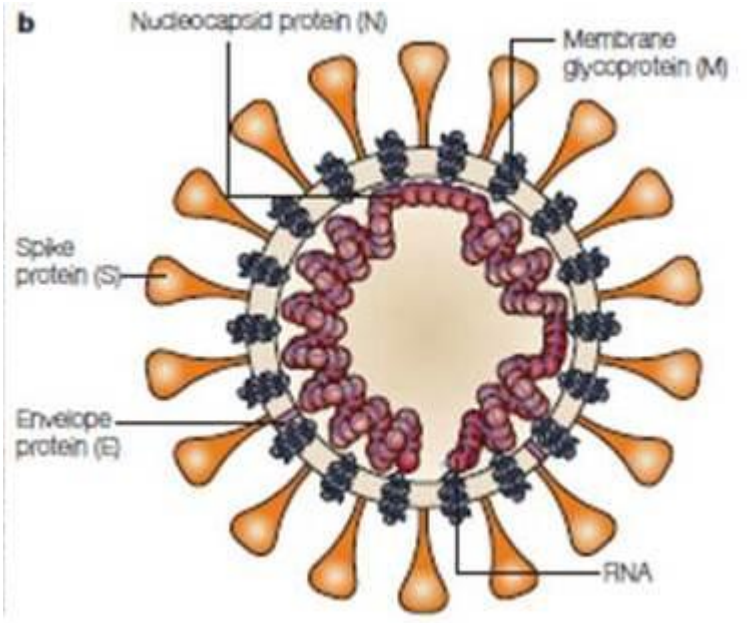
- Is divided into 4 genera
    1. Alphacoronavirus
    2. **Betacoronavirus**
    3. Gammacoronavirus
    4. Deltacoronavirus

Coronaviruses

- Enveloped RNA viruses with positive-sense, single stranded RNA genomes
- With a crown-like appearance under an electron microscope (coronam is the Latin term for crown)
- Diameter of approximately 60-140 nm
- The genomic structure is organized in 30 000 bases (the larges known RNA viruses)
- Circulate among animals with some of them also known to infect humans
    - These viruses can cross species barriers and can cause illness in human

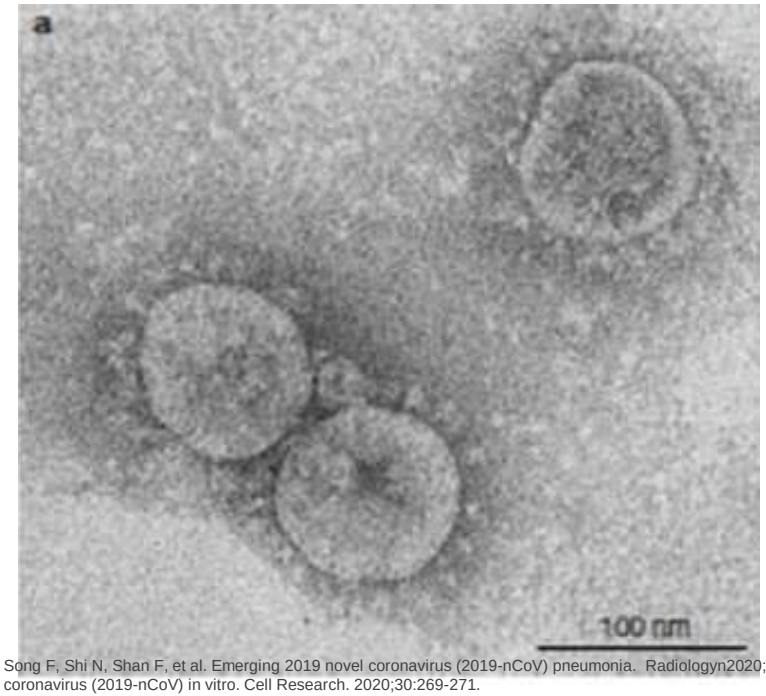
Song F, Shi N, Shan F, et al. Emerging 2019 novel coronavirus (2019-nCoV) pneumonia. Radiologyn2020;00:1-8. doi.org/10.1148/radiol.2020200274. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Research. 2020;30:269-271.

# The family Coronaviruses




- Are responsible for about 5%-10% of acute respiratory infections in hunans

- **Bads** – are considered as natural hosts of these viruses, several other species of animals are also known to be a source




- Three zoonotic CoVs-β cause severe respiratory diseases
  - **SARS-CoV**
  - **MERS-CoV**
  - **SARS-CoV-2**
    - Is genetically closely related to the SARS-CoV
    - CoV genome is highly conserved. SARS-CoV-2 and SARS-CoV share similar key protein include the spike protein, RdRp, 3CLpro and PIpro

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# Severe Acute Respiratory Syndrome (SARS)

- Etiologic agent – **SARS-CoV (SARS-CoV-1)**
- Was transmitted to humans from the Himalayan civet cats
- Appeared in the Guangdong province of southern China in 2002
- These epidemic was in 2-7/2003 (8437 patients/813 deaths)

- It was mainly characterized by flu-like symptoms, including high fevers exceeding 38 C, myalgia, dry nonproductive dyspnea, lymphopaenia, infiltrate on chest radiography
- In 38 % of all cases, the resulting pneumonia led to acute breathing problems requiring artificial respirators
- The overall mortality rate was about 10%, but mortality rate in the elderly was as high as 50%
- SARS affected relatively few children and generally appeared to be milder in the paediatric age group
- **Reproduction number (R) = 3**
  - On average, each patient transmits the infection to an additional 3 individuals

Stadler K, Masignani V, Eickmann M, et al. SARS-beginning to understand a new virus. Nature reviews, microbiology. 2003;1:209-218.

# Middle East Respiratory Syndrome (MERS)

- Etiologic agent – **MERS-CoV**
- Was transmitted to humans from the dromedary camel
- This epidemic began in Saudi Arabia in 2012 and still causes as sporadic cases
- It is now seen sporadically year-round but more so during wintertime
- There were 2494 cases/858 deaths in 2012
- The overall mortality rate was about 34%, but mortality rate in the elderly was as high as 50%
- R = 1

Stadler K, Masignani V, Eickmann M, et al. SARS-beginning to understand a new virus. Nature reviews, microbiology. 2003;1:209-218.

# COVID-19

- Currently, the whole world is facing the largest epidemic caused by coronaviruses, which has been identified as

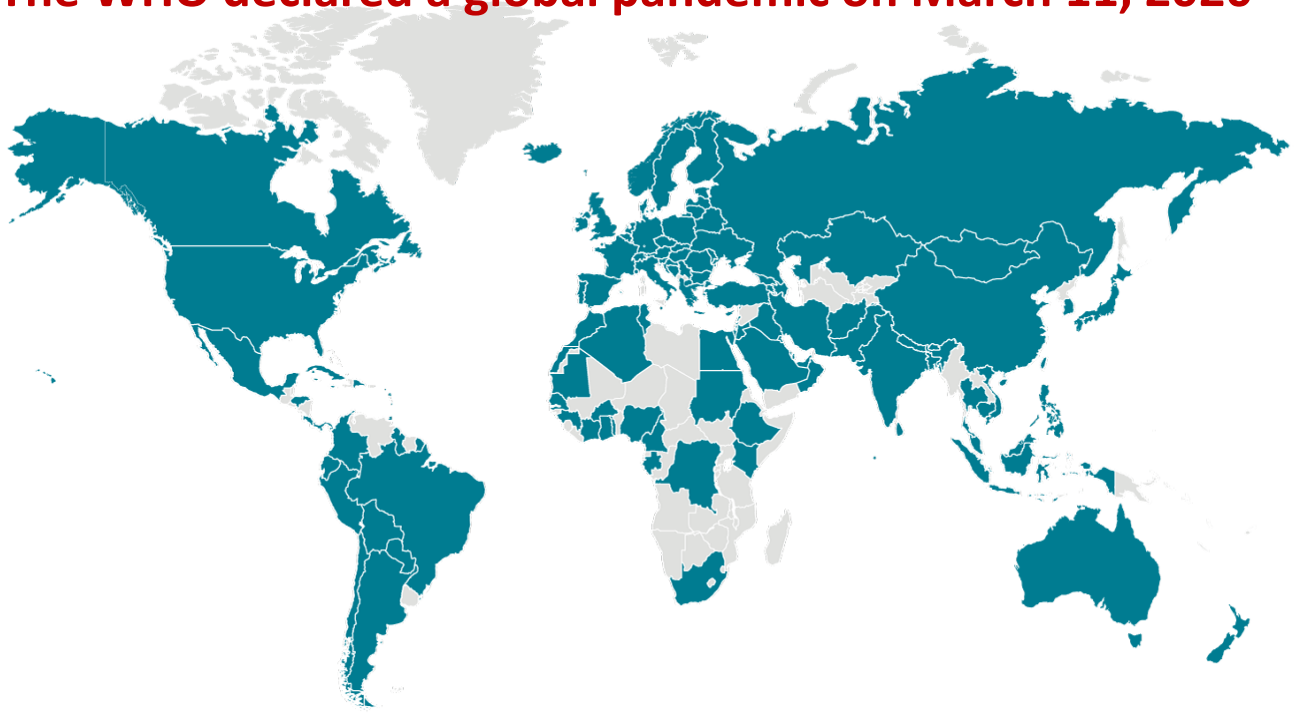
  - **Coronavirus disease 2019 (COVID-19)**

    - is the name given to the disease associated with the new virus
  - **SARS-CoV-2**
    - Severe Acute Respiratory Syndrome Coronavirus-2
    - Is the name given to the 2019 novel coronavirus
    - Is a new strain of coronavirus that has not been previously identified in humans
    - Is the third documented spillover of an animal coronavirus to humans in 2 decades that has resulted in a major epidemic
    - Available data suggested that the SARS-CoV-2 may be less virulent than the SARS-CoV and MERS-CoV.

www.ecdc.europa.eu/en/novel-coronavirus-china/questions-answers; Guo et al. The origin, transmission and clinical therapies on coronavirus disease 2019 /COVID-19) outbreak – an update on the status. Military Medicine Research. 2020:7:11.

# COVID-19

- **In December 2019,** a cluster of pneumonia cases, caused by a newly identified β-coronavirus, occurred in Wuhan, in China
- The epidemic broke out possibly related to a seafood market from where it then spread from person to person
- This new virus seems to be very contagious and has quickly spread globally
- **The WHO declared a global pandemic on March 11, 2020**



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# COVID-19 transmission

- The first cases of the COVID-19 disease were linked to direct exposure to the seafood market of Wuhan
  - The animal-to-human transmission was presumed as the main mechanism
- Subsequently, virus was transmitted **from person-to-person**
- The virus seems to be transmitted mainly via **respiratory droplets that people sneeze, cough, or exhale**
- Particles can be detected in upper and lower respiratory tracts
- A relatively low infective dose is required to transmit the infection
- Transmission can still occur during asymptomatic stage
  - This transmission may represents 25-50% of total infections.
- The virus can also survive for several hours on surfaces such as tables, door handles…
- More stable on plastic and stainless steel than on copper and cardboard, and viable virus was detectable ≤72 hours

- More over SARS-CoV-2 was isolated from **fecal swabs and blood** – indicating the possibility of multiple routes transmission

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# COVID-19

- SARS-CoV-2 exhibits strong infectivity but less virulence, compared to SARS and MERS

## Contagiousness

- Is probably higher than for seasonal influenza
  - **The basic reproduction number (R)**
    - Of SARS-CoV-2 to be around 2.2 or even more

      (range from 1.4 to 6.5)
    - It means, that one infected person will infect between 2-3 another people

## ECDC estimats that mortality rate

- Seasonal influenza
  - Approximately 1 people die in every 1000 people who are infected
- The current estimated mortality rate for COVID-19
  - Is 20-30 per 1000 people
    - It is significantly less than the 2003 SARS outbreak

www.ecdc.europa.eu/en/novel-coronavirus-china/questions-answers; Guo et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status. Military medical Research, 2020;

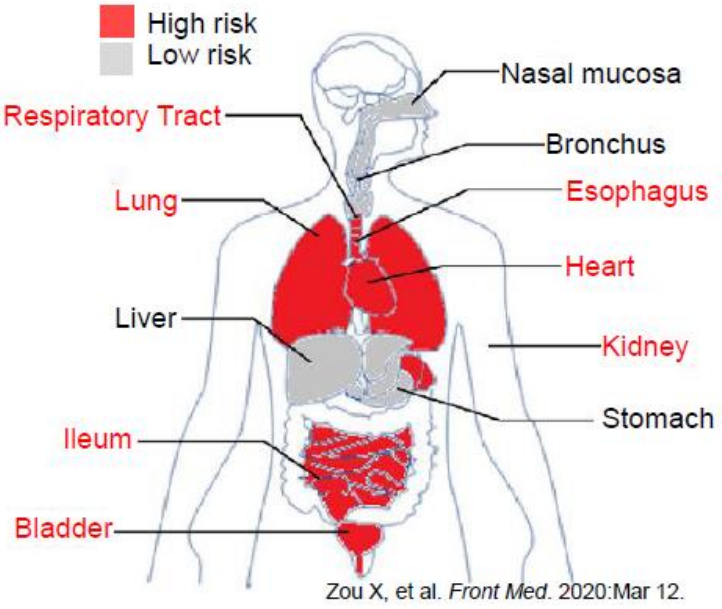
# Potential Organ Vulnerability to SARS-CoV-2 based on ACE2 Receptor Distribution

- SARS-CoV-2 utilizes ACE2 receptor for entry into host cell[1,2]
- SARS-CoV-2 has a strong binding affinity to the human cell receptor, angiotensin-converting enzyme 2 (ACE2)[3]

**Affinity of SARS-CoV-2 to ACE2 receptors and distribution of these host receptors may potentially have a role in organ vulnerability**

ACE2 protein presents in abundance on lung alveolar epithelial cells and enterocytes of small intestine

**Risk Map Showing Vulnerability of Different Organs to SARS-CoV-2 Infection[3]**




Zou X, et al. *Front Med*. 2020:Mar 12.

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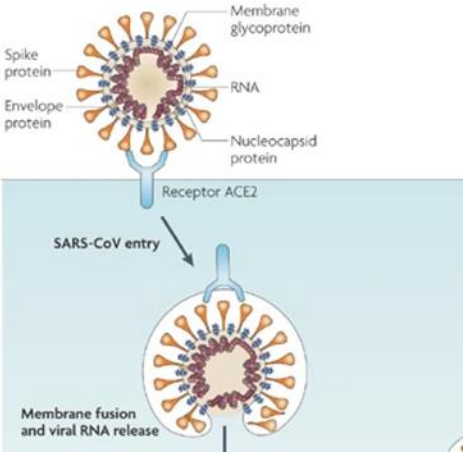
**Angiotensin converting enzyme II (ACE2)**

- Is a known cell receptor for SARS-CoV
- It is clear now that SARS-CoV-2 could use angiotensin-converting enzyme 2 (ACE2), the same receptor as SARS CoV

- The binding of SARS-CoV-2 spike (S) glycoprotein and ACE2 receptor is a critical step for virus entry

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# COVID-19

**The incubation period** for COVID-19

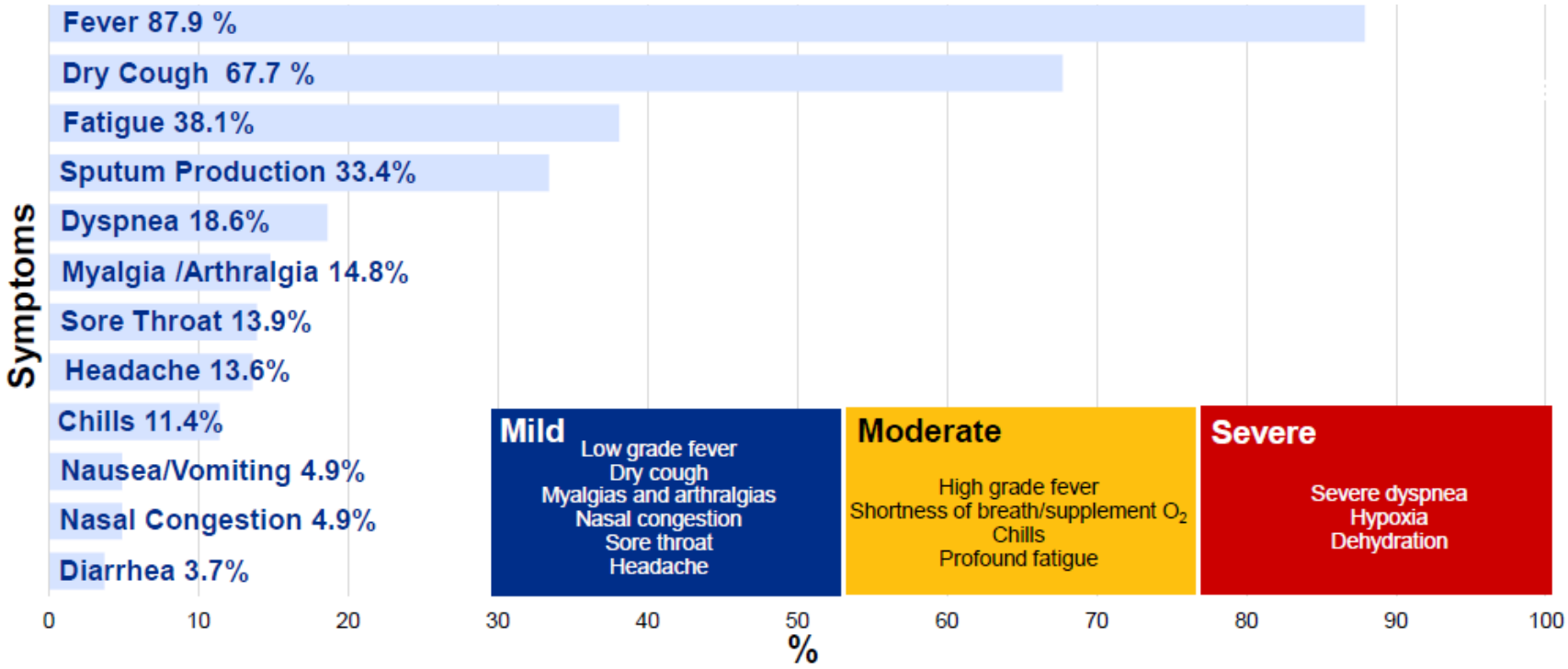
- The time between exposure to the virus and onset of symptoms
- Is currently estimated at between 2 and 14 days

## The clinical manifestations

- **Mild disease**
  - Fever, cough, flu-like illness….
  - This occurred in 81% of cases and most patients have a good prognosis
- **Severe disease**
  - With severe pneumonia
  - This occurred in 18% of cases
- **Critical disease**
  - Respiratory failure, septic shock, multiple organ dysfunction…
  - This occurred in 5% cases

www.ecdc.europa.eu/en/novel-coronavirus-china/questions-answers. Huang et al. Lancet 2020.

# COVID-19 Clinical Presentation




**Disease severity can be differentiated based on symptom presentation in patients with COVID-19**

**Fever and cough**

- are the dominant symptoms

**Gastrointestinal symptoms**

- Herald more serious disease and suggesting the differences in viral tropism as compared with SARS-CoV, MERS-CoV and influenza

# COVID-19 complications

- Most patients have a good prognosis
- About 20% of patients have severe illness with complications
  - Acute respiratory distress syndrome (ARDS)
  - Arrhytmia
  - Shock
  - Acute kidney injury
  - Acute cardiac injury
  - Liver dysfunction
  - Secondary infection…

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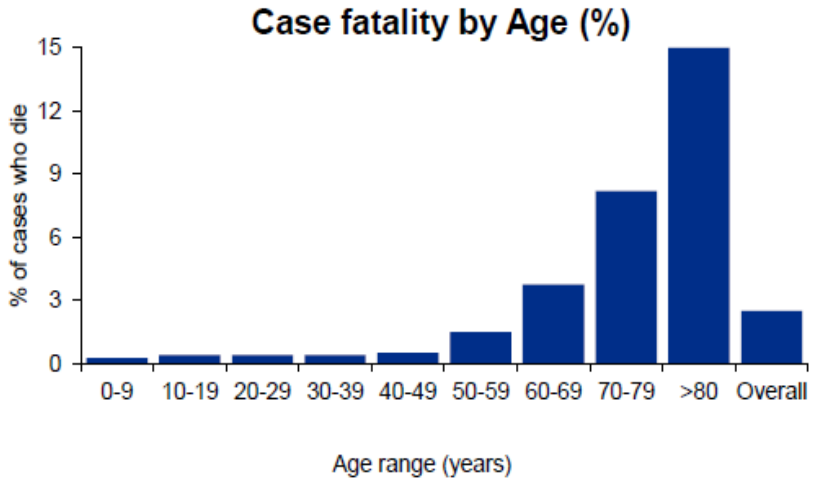
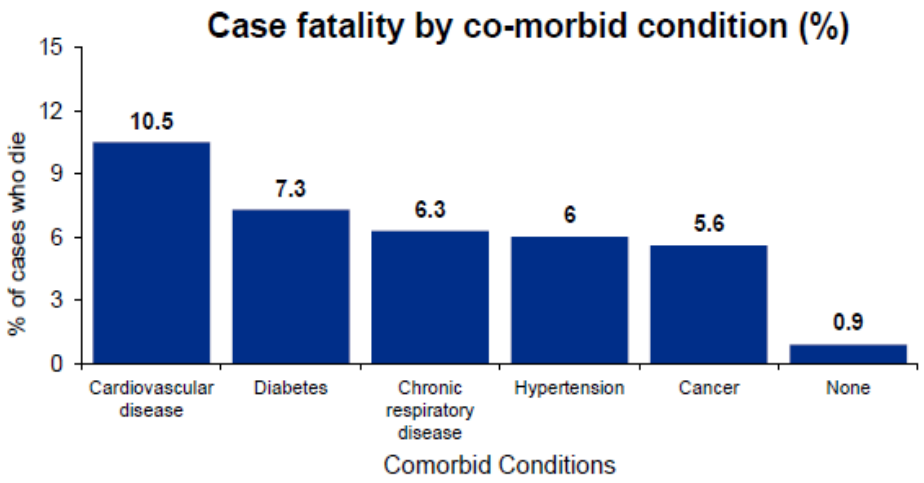
# Case Fatality Rate Based on Age and Comorbidities




**The global case fatality rate for COVID-19 infected patients may be as high as 3% and disproportionally affects those of older age and those with comorbidities**

## Elderly people

- And those with underlying health conditions (e.g. hypertension, diabetes, cardiovascular disease, chronic respiratory disease, cancer…)
- Are considered to be more at risk of developing severe symptoms
- Developed rapidly into acute respiratory distress syndrome, septic shock, metabolic acidosis hard to correct and coagulation dysfunction, even leading to the death

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# COVID-19 CT imaging

- After an incubation period of 2-14 days - very early changes on CT of the lungs
- Abnormalities are already at an early stage in most patients
- The main findings
  - Pure **ground-glass opacities (GGO),** GGO with reticular and/or interlobular septal thickening, and GGO with consolidation
  - The absolute number of lung findings increased with the time from symptom onset
  - The younger patients tended to have more GGOs, while older patients tended to have more areas of lung involvement and more **consolidation**
- A part of confirmed patients appeared the normal CT image presentations

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Hosseiny M et al. Radiology perspectives of coronavirus disease 2019 (COVID-19). Am J Roentgenology, 2020; DOI: 10.2214/AJR.20.22969

# CT scan COVID-19

Consolidation

- Indicated disease progression or more severe disease

Most pulmonary lesions involved

- Bilateral lungs with multiple lung lobes
- With predominant distribution in posterior and paripheral part of the lungs
- The posterior and paripheral lung predominant distribution – ussually is charakteristic

Patients with fever and/or cough and with GGO-prominent lesions in the peripheral and posterior part of lungs on CT images, combined with normal or decreased white blood cells should be highly suspected of having COVID-19 pneumonia.

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# RT-PCR Diagnosis of SARS-CoV-2

- RT-PCR is the gold standard diagnostic test
  - High specificity*
  - Variable sensitivity depending on test*

**Specimen Collection Sites**

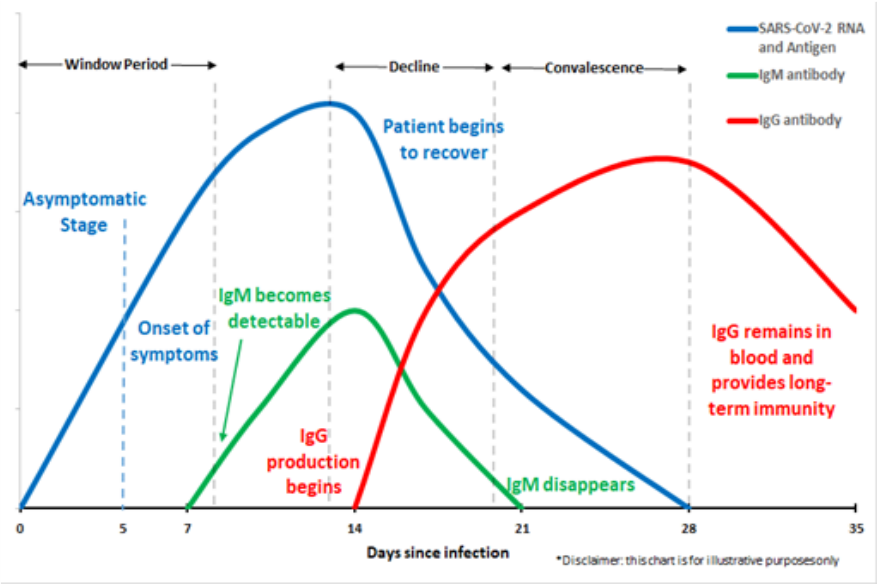
| Collection site | Purpose |
|---|---|
| URT: nasopharyngeal (NP) and oropharyngeal (OP) | WHO and US CDC recommend NP swab collection for initial diagnostic testing |
| LRT: expectorated sputum, endotracheal aspirate, or bronchoalveolar lavage in ventilated patient | If URT specimens are negative and clinical suspicion of SARS-CoV-2 remains |

## ELISA tests

- Tests are currently in development detection of IgM and IgG antibodies against SARS-CoV-2 proteins
- Seroconversion for IgM antibodies occurs a few days earlier than IgG
  - IgM: 5 days (3-6)
  - IgG: 14 days (10-18)

Most but not all patients recovered from COVID-19 producing neutralizing antibodies that are likely sufficiently protective against infection.

But **immunity may not be long-lasting** (1-3 years) based on work with routine coronaviruses, SARS and MERS.



# COVID-19 laboratory examination

Most of the patients had

- Normal or decreased neutrophil count
- Lymphocyte count was low (or normal) or continued decrease
- Elevate D-dimer
- LDH may be modestly elevated
- Elevated IL-6
- C-reactive protein is elevated
- Thirty-one patients had a low CD4+ cell count
  - with a range of 72-408 cells/μl

- Elevations in IL-6, CRP, ferritin suggested correlating with a cytokine storm and impending ARDS.

# COVID-19 therapy

SARS-CoV-2 = as it is a new virus

- **Nobody has prior immunity**
  - which in theory means, that entire human population is potentially susceptible to COVID-19 infection
- Unlike influenza, there is no vaccine
- No specific treatment for the disease
- Healthcare providers treat the clinical symptoms of patients
- **Supportive care**
  - e.g. fluid management
  - oxygen therapy – major treatment intervention
  - intubation and protective mechanical ventilation – may be necessary in cases of respiratory failure refractory to oxygen therapy
  - ECMO (extracorporeal membrane oxygenation) – to patients with refraktory hypoxemia
  - hemodynamic support – is essential for managing septic shock

www.genengnews.com/a-lists/how-to-conquer-coronavirus-top-35-treatments-in-development/

# COVID-19 candidate therapies

- Currently there are no licensed therapeuticm agents for the treatment of COVID-19
- There is an increasing number of antiviral agents being investigated in clinical trials for the treatment of COVID-19
  - **Remdesivir** (anti-SARS-CoV-2 nukleoside inhibitor)
    - Shows broad spectrum antiviral aktivity against several RNA viruses
    - Remdesivir is a prodrug, an adenosine analog that acts as an inhibitor of RNA-dependent RNA polymerases (RdRps). Remdesivir-TP competes with adenosine-triphosphate for incorporation into nascent viral RNA chains. Once incorporated into the viral RNA. Because RDV-TP does not cause immediate chain termination, the drug appears to evade proofreading by viral exoribonuclease (an enzyme thought to excise nucleotide analog inhibitors).
  - **Hydroxychloroquine** (antimalaria)
    - Mechanisms may include inhibition of viral enzymes or processes such as viral DNA and RNA polymerase, viral protein glycosylation, virus assembly, new virus particle transport, and virus release. Other mechanisms may also involve ACE2 cellular receptor inhibition, acidification at the surface of the cell membrane inhibiting fusion of the virus, and immunomodulation of cytokine release.

www.genengnews.com/a-lists/how-to-conquer-coronavirus-top-35-treatments-in-development/

# COVID-19 candidate therapies

- **Lopinavir/ritonavir** (boosted HIV protease inhibitor)
  - Lopinavir and ritonavir may bind to Mpro, a key enzyme for coronavirus replication. This may suppress coronavirus activity
    - + /- interferon beta (immunomodulator)

- Various protease inhibitors, oseltamivir (neuraminidase inhibitor), favipiravir (RdRp inhibitor), chloroquine… are investigatet to treatment COVID-19

- **Azithromycin**
  - Macrolides may have immunomodulatory properties in pulmonary inflammatory disorders. They may downregulate inflammatory responses and reduce the excessive cytokine production associated with respiratory viral infections; however, their direct effects on viral clearance are uncertain. Immunomodulatory mechanisms may include reducing chemotaxis of neutrophils (PMNs) to the lungs by inhibiting cytokines (i.e., IL-8), inhibition of mucus hypersecretion, decreased production of reactive oxygen species, accelerating neutrophil apoptosis, and blocking the activation of nuclear transcription factors.

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# COVID-19 candidate therapies

- **Tocilizumab**
  - Tocilizumab inhibits IL-6-mediated signaling by competitively binding to both soluble and membrane-bound IL-6 receptors. IL-6 is a proinflammatory cytokine that is involved in diverse physiological processes such as T-cell activation, immunoglobulin secretion induction, hepatic acute-phase protein synthesis initiation, and hematopoietic precursor cell proliferation and differentiation stimulation. IL-6 is produced by various cell types, including T- and B-cells, lymphocytes, monocytes, and fibroblasts.

- **COVID-19 Convalescent Plasma or serum-containing neutralizing antibodies against SARS-CoV-2**
  - Plasma collected from persons who have recovered from COVID-19 that may contain antibodies to SARS-CoV-2. Clinical trials are being conducted to evaluate the use of COVID-19 convalescent plasma to treat patients with severe or immediately life-threatening COVID-19 infections. COVID-19 convalescent plasma is not intended for prevention of the infection.

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# COVID-19 therapy

- **Corticosteroids**
  - Corticosteroid therapy is not recommended for viral pneumonia; however, use may be considered for patients with refractory shock or acute respiratory distress syndrome.

- **NSAIDs**
  - The FDA continues to investigate the use of NSAIDs in patients with COVID-19 symptoms.
  - Concern for potential worsening of COVID-19 symptoms has been suggested, but confirmatory clinical data is lacking at this time. There is an anecdotal published letter that suggests a link between ibuprofen and increased ACE2 expression that may lead to worse outcomes in COVID-19 patients.
  - Acetaminophen may be considered for temperature control.

- Various research efforts are currently underway to develop effective drugs and a vaccine against COVID-19

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# Prevention
# How can I avoid getting infected

- Personal protection and hygiene measures
    - Wearing masks
    - Hygiene and desinfection

- The virus enters into the human body via **eyes, nose and/or mouth**
    - So, it is important to avoid touching your face with unwashed hands
    - **Washing of hands** with soap and water for at least 20 seconds
        - Cleaning hands with alcohol-based solutions, gels or tissues is recommended in all settings
    - Desinfect frequently touched household objects

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# The epidemiological measures

Public health measures aimed at reducing contact rates in a population and thereby reducing transmission of the virus

- **Isolation of patients and quarantine of exposed contacts**
- **Social distancing measures**
    - Maintaining distance from others min. 2 meters
    - Avoid crowding
    - Closing scholls and childcare centers
    - Simultaneous use of multiple measures to reduce social mixing
- Measures for persons entering or exiting an infected area

# Conclusion

Unfortunately, it is not possible to predict

- how long the outbreak will last and how the epidemic will unfold.

We are dealing with a new virus and therefore a lot of uncertainty remains.

For instance, it is not known whether transmission within the EU/EEA will naturally decrease during the northern hemisphere summer, as is observed for seasonal influenza.