COVID-19 infection

Current outbreak: COVID-19

- At the end of 2019, possibly even earlier 1, a new coronavirus infection emerged in Wuhan, China. By the time this text was last updated, over 238 million laboratory-confirmed cases have been found worldwide and over 4.8 million persons have died. The actual number of infections is considerably higher.
- In Europe, the highest number of cases has been found in the UK (over 8 million cases) and Russia, Turkey and France (over 7 million cases in each).
  - Virus variants have developed from the original virus, such as the Alpha variant (B.1.1.7), Beta variant (B.1.351)., Gamma variant (P.1) and Delta variant (B.1.617). Due to its highest infectivity, the Delta variant is becoming the predominant virus in many countries. See also the (global) Variants Surveillance by the CDC 2 and (for Europe) the section "Variants of concern" in 3 and the SARS-CoV-2 Variants Dasboard 4 by the ECDC.
  - As the immunization coverage increases, it has been suggested that the main attention in curbing the spread of the virus should be put on the workload of hospitals instead of on the number of new infections. In countries with good immunization coverage, symptomatic infections have shifted to younger age groups and an increasingly higher share of hospitalizations concern people below 60 years of age.
- Globally, the pandemic is still spreading; for the time being, the highest numbers of new infections are recorded in the United States (over 44 million cases), in India (over 33 million cases), in South America (particularly in Brazil, over 21 million cases), and in many European countries (in total over 72 million cases).
  - Following a mutation in their spike protein, the virus variants Alpha, Beta, Gamma and Delta are more infectious than the original virus and may cause more severe symptoms. In a study comparing the mortality in infections caused by the Alpha variant and the original virus strain, the risk of death from infections with the Alpha variant within 28 days was found to be 64% higher 5.
- Before COVID-19 vaccines became available, results from a number of European countries indicated that the level of seropositivity against the virus in the population was generally low (< 10%) and regional variation existed 6, suggesting that without vaccination a rapid development of so-called herd immunity was unlikely to take place even in countries with a high number of COVID-19 infections. Vaccinations are changing the situation, but important uncertainties remain concerning immunity on the population level 7 8 9 10.
- Current information on the pandemic spread is available from the following sources:
  - WHO weekly epidemiological and operational updates (world) 11
  - ECDC COVID-19 Situation Dashboard 12
  - CDC COVID-19 Data and Surveillance 13
  - Visualizations: WHO (world) 14, WHO (Europe) 15 and the Johns Hopkins University (world) 16
- Notice that all information concerning COVID-19 is possibly subject to rapid changes. Consult official sources especially for epidemiological data and criteria for selecting patients that should be investigated for the infection.
- The ECDC has published guidance on prevention and control measures in primary care, including general practitioner practices, dental clinics and pharmacy settings 17 and more generally in healthcare settings 18.
- See also other international sources (e.g. WHO, ECDC, CDC) listed in references below.

Essentials

- The clinical picture of COVID-19 infection varies from asymptomatic or mild respiratory infection or gastroenteritis to a difficult-to-manage pneumonia that may be complicated by acute respiratory failure.
- Thromboembolic complications are more common than in most other respiratory infections.

- Disease with severe symptom picture is more common in the elderly population, but severe and life-threatening symptom picture may occur also in middle-aged persons, very rarely in younger age groups.
- Initially, a specimen to confirm coronavirus infection and, based on clinical consideration, other specimens required in the differential diagnosis to detect also other possible infections should be collected and relevant examinations performed (sputum, blood, acute and convalescent serums, urine, chest x-ray).
- Acute COVID-19 infection is diagnosed with a PCR or antigen test of a nasopharyngeal sample. Antibody tests allow investigation of patient's immunity. Tests are associated with sources of error that always must be taken into account when interpreting the results.
- Close contacts of all suspected cases should be traced and information relating to quarantine procedures and other precautions should be given.
- A patient with mild symptoms is cared for at home. The patient should be informed about the possible worsening of symptoms and given instructions for such cases.
- When a serious coronavirus infection is suspected, the patient must be referred to an infectious disease ward for care and monitoring, whilst maintaining strict contact and droplet isolation precautions. If possible, airborne infection isolation should also be instituted at the hospital.
- In a convalescent patient, the end of infectiousness can be ensured by control specimens or by allowing an adequately long time to pass after clinical recovery.

Epidemiology

- Common coronaviruses generally cause mild upper respiratory tract infections.
- The SARS (Severe Acute Respiratory Syndrome) epidemic that originated in China in 2003 infected about 8 000 individuals, of whom about one in ten died.
- A new previously unknown SARS-like coronavirus known as MERS (Middle East Respiratory Syndrome Coronavirus, MERS-CoV) was identified in September 2012.
- The pathogen of COVID-19 infection (SARS-CoV-2) resembles greatly that of the coronavirus epidemic in 2003.
- Coronaviruses are transmitted through close contact with secretions or droplets.
  - Also COVID-19 infection is transmitted primarily through droplets and direct contact. There is no certainty about transmission through aerosols, but also transmission through airborne route is considered possible under special circumstances, such as in closed spaces with insufficient air ventilation or with air recirculated without appropriate filtering, or through exposure to respiratory particles generated during physical exercise or singing [19] [20] [21] [22] [23] [24].
  - New variants of the SARS-CoV-2 are more infectious than the original strain of the virus, and at least the UK variant is associated with higher mortality than the original virus strain [5]. In areas where the new mutations have been able to spread, a very rapid increase in the number of cases has been observed despite restrictive measures.
  - It is advisable to keep a clearly longer than the usual 1-meter distance from a coughing or sneezing person.
- Health care personnel looking after patients with coronavirus infections in hospitals and other care facilities form a particular risk group.

Clinical presentation

- Due to the epidemiological situation, this section focuses on the clinical presentation of COVID-19 infections.
- None of the symptoms are specific. The disease may even be asymptomatic or produce no fever and resemble a mild respiratory tract infection.
- Incubation time is 2–14 days, typically 4–5 days.
- The symptomatic form of the disease often starts with sudden high fever (> 38.5 °C) and cough.
- The risk of thromboembolic complications is considerably higher than in the usual respiratory infections.
- When assessing patients' symptoms, especially remotely (over the phone or online, for example), keep in mind that the stress caused by an acute infection may exacerbate possible underlying primary

diseases. The symptoms may be caused by exacerbated coronary artery disease or diabetes, for example.

- The clinical picture varies significantly according to the age group of patients. Severe clinical picture is more common in elderly patients (age over 70 years), who often have some primary diseases. A disease with severe symptoms is, however, possible also in younger, otherwise healthy individuals.
- In children and adolescents the disease is nearly always mild.
  - However, a hyperinflammatory syndrome (Multisystem Inflammatory Syndrome in Children, MIS-C) has been described in paediatric and adolescent patients . The symptom picture includes fever, laboratory findings suggesting inflammation, and a severe disease of one or more organ system(s), requiring hospital care. A severe cardiac failure and circulatory insufficiency requiring intesive care develops in up to half of these patients [12].
- The following groupings describe clinical pictures according to Finnish data.
- Mild or moderate clinical picture, patient in home care
  - About 95% of patients below 50 years, about 92% in age group 50–59 years, and about 88% in age group 60–69 years.
  - In older age groups the symptom picture becomes more severe, and not being hospitalized does not describe the severity of disease since some patients with severe symptoms do not end up in hospital.
  - Typical symptoms include cough, fever and respiratory difficulties.
  - Active surveillance of the epidemic requires low threshold in testing for COVID-19. Consequently, all febrile patients in home care should get tested for COVID-19, unless another cause for the fever is known with certainty.
  - The disease may be non-febrile and resemble a common cold, or it may be completely asymptomatic. The prevalence of an asymptomatic infection is not known.
  - Further symptoms that have been observed include gastrointestinal symptoms (nausea, diarrhoea), myalgia, headache, vertigo, sore throat, and, more rarely, loss of the sense of smell or taste and cutaneous vasculitis-like lesions.
- Disease requiring hospital care
  - About 1–2% of patients below 40 years, about 4% in age group 40–49 years, about 7% in age group 50–59 years, about 12% in age group 60–69 years, and about 20% in patients over 70 years of age. Part of the eldest age group does not end up in hospital despite a severe disease.
  - The worsening of symptoms often takes place at about 5 days after symptom onset.
  - The patients have dyspnoea and high fever.
  - A chest x-ray will show bilateral diffuse infiltrates typical for viral pneumonia (not a lobar pneumonia). In a hospital setting, the lungs are often investigated by performing a pulmonary CT scan.
  - Thromboembolic complications are common.
- Disease requiring intensive care
  - Less than 1% of patients below 50 years, about 1% of patients below 60 years, about 3% of patients below 70 years. Part of the eldest age group does not end up in hospital despite a severe disease.
  - The disease may develop into acute respiratory distress syndrome (ARDS).
  - Multiple organ damage may develop, including e.g. renal failure.
  - Cardiac symptoms may occur (arrhythmias, myocarditis).
- Mortality
  - Sporadic cases in patients below 50 years, about 0.2% in age group 50–59 years, about 3% in age group 60–69 years, about 4% in age group 70–74%, about 13% in age group 75–79, about 27% in patients over 80 years of age.
- Significant differences in the aforementioned percentages may apply between countries, depending, for example, on treatment protocols, available health care resources and the epidemic situation.

Diagnosis

- WHO has issued guidance on emergency use of ICD codes, see 25 and national guidance.
- The laboratory investigations carried out because of suspected COVID-19 infection must not delay other diagnostic investigations and treatment of a person who has gotten seriously ill.

- Acute infection
  - The patient is referred for investigations according to regional and local guidelines. In Finland, a health care professional first takes the patient history and asks about symptoms and then assesses the need for testing.
  - It may be necessary to contact the sample collection site before taking the test and requesting analysis.
  - An acute COVID-19 infection is usually diagnosed with a PCR or antigen test of a nasopharyngeal sample.
    - Sources of error include, among others, deficient specimen collection technique and the virus not occurring in the area where the sample is taken from.
    - The PCR test result takes about 12–24 hours to be ready, but there are also rapid tests available.
    - Viral RNA may already be detectable by a PCR test some days before the onset of symptoms, but during that time the rate of false negative results is, however, considerable. The proportion of false negatives is at its lowest within one week from the onset of symptoms (about 20%), after which their proportion starts to rise again little by little within the following 2 to 3 weeks [9].
    - Overall, viral antigen tests are less sensitive than nucleic acid detection tests. The advantage of antigen tests compared with PCR tests include their speed and ease-of-use, as well as lower unit price.
  - New home tests to be used by non-professionals have become available. Their accuracy is clearly inferior to that of tests performed in a laboratory. In addition to false negative results, also false positive results will constitute a problem especially in situations where the prevalence of the disease in the population is low. A positive test result must always be verified with a PCR test performed in health care.
- For COVID-19 testing, see 1.
- There may be national differences in the approach regarding suspected cases. See also locally available instructions on when and whom to test for COVID-19 and when and whom to consult.
- Determination of antibodies
  - Antibodies against coronavirus usually begin to develop during the 2nd week of being ill, and IgM/IgG seroconversion has taken place in almost all patients (in more than 90%) by the 3rd or 4th week of being ill C. There is no definite data on the persistence of the antibodies, but they seem to prevail for at least several months after the infection 26.
  - In a Finnish study conducted by the National Institute for Health and Welfare, neutralizing antibodies persisted still at 12 months after the infection in the majority of COVID-19 patients (see preprint in 27).
  - Tests to detect antibodies against coronavirus in the blood cannot be used to diagnose an acute infection, due to the delay between the onset of the infection and the formation of antibodies. Instead, they aim at providing an answer to the question whether a person has had a COVID-19 infection.
    - Problems include false negative results (sensitivity) when the level of antibodies in a patient is low, as well as false positive results (specificity), when the prevalence of the infection in a population is low.
    - For the time being, determining antibodies to detect an earlier COVID-19 infection or the presence of immunity is not recommended.

Treatment

- Due to the current epidemic, this chapter focuses on the treatment of COVID-19 infection.

Home care

- The principles in the treatment of a patient in home care with rather mild symptoms do not differ from those applied in a regular respiratory infection.
- The focus of care is on non-pharmacological treatment, such as rest, adequate nutrition and intake of fluids.
- Pain-reducing and antipyretic medication (paracetamol, NSAIDs) may be used, as required.

- Severe nausea may be treated with metoclopramide or prochlorperazine, see article on Nausea and vomiting .
- In home care, thromboprophylaxis is considered individually in patients known to have an increased risk of thrombosis. Blood clotting tests are not performed routinely in patients whose condition allows home care.
- If the symptoms of a patient with COVID-19 infection become more severe or prolonged, laboratory tests (basic blood count with platelet count, plasma creatinine (GFR 1), ALT, D dimer (> 1.5 mg/l predicts progression of the disease), prothrombin time or INR, and CRP, for example) and/or imaging studies are performed based on clinical consideration, unless the patient is referred directly to a hospital for assessment. Remember that the clinical state of a patient with COVID-19 may deteriorate and become critical within hours, and hence the threshold for referring a patient to hospital should be kept at a sufficiently low level.
- Symptoms that warrant hospital care to be considered include, among others, high fever and fatigue, dyspnoea, and deterioration of general condition. It is typical for COVID-19 infection that symptoms worsen after being ill for 5–7 days.

Thromboprophylaxis

- An acute COVID-19 infection is associated with increased activation of the blood coagulation system.
- Find out about and consult any national or regional advice and recommendations on thromboprophylaxis.
- An increasing D dimer level predicts the development of acute respiratory distress syndrome (ARDS), multiple organ dysfunction and mortality.
- An increase in the D dimer level to 3–4-fold of the normal (< 0.5 mg/l) level is an indication for hospital care in patients with prolonged COVID-19 infection and bed rest.
  - This applies especially in patients belonging to risk groups for COVID-19 and venous thrombosis, and who generally are the same patients.
  - For an algorithm for the management of coagulopathy in COVID-19, see also Figure 1 in 28.
- Due to the increased coagulability of blood, the incidence of pulmonary embolism and deep vein thrombosis increases (in 18% of hospitalized patients and up to 30% of patients requiring intensive care). Pneumonia or oxygenation disturbances caused by COVID-19 infection may mask the symptoms of pulmonary embolism.
- Also, arterial occlusions and organ damage caused by occlusions in small vessels may occur (e.g. heart and kidney failure).
- Heparin therapy prevents coagulation and alleviates inflammation. Thromboprophylaxis with LMWH is recommended to all patients in hospital care and in home care to patients with risk of thrombosis, unless there are contraindications to it.
- Thromboprophylaxis (with e.g. enoxaparin, dalteparin or tinzaparine) should be considered especially in the following patients if they are not already under anticoagulant or antithrombotic therapy:
  - patients in hospital care
  - during pregnancy and postpartum (6 weeks after delivery)
    - consult a gynaecologist or an obstetrician concerning the need and choice of prophylactic medication
  - patients in home care with
    - factors that predispose to thrombosis (e.g. obesity, dehydration, immobilization, cancer, inflammatory and myeloproliferative primary diseases, cardiovascular diseases, thrombophilia, diabetes with poor control, earlier venous thrombosis or pulmonary embolism, recent surgery or recent episode of acute hospital care due to severe disease [e.g. sepsis])
    - severe symptoms (e.g. high fever) associated with immobilization due to weak overall condition
  - The decision regarding thromboprophylaxis is made on clinical grounds taking into account the patient's age, overall health and functional capacity as well as his/her bleeding risk. See also .
- In the acute phase of COVID-19 infection, direct anticoagulants (DOACs; dabigatran, apixaban, edoxaban, rivaroxaban) are not recommended for the prophylaxis or treatment of thromboembolism.
  - Through their action on tissue level, DOACs may unexpectedly trigger alveolar haemorrhage, for example, and their benefit in preventing venous thrombosis in not proven in medical (non-surgical) patients.

Respiratory insufficiency

- Patients with more severe symptoms, requiring hospital care, often need, for example, supplemental oxygen and other supportive treatments, for instance antimicrobial pharmacotherapy for a potential secondary bacterial pneumonia. Risk of thrombosis is increased and usually a prophylactic LMWH therapy is started, see above.
- In severe respiratory insufficiency, ventilator therapy, treatment of septic shock.

Pharmacotherapy

- Remdesivir has been approved for the treatment of COVID-19 infection with severe symptoms. The final results of the trial ACTT (Adaptive COVID-19 Treatment Trial) have been published 29. According to a meta-analysis carried out in the SOLIDARITY trial, remdesivir decreases the relative risk of death by 9%, 95% CI -21 – +5%. According to the meta-analysis, remdesivir decreases hospitalization period by about 1–2 days.
- The results of the SOLIDARITY trial indicate that in hospitalized patients treatment with hydroxychloroquine, lopinavir, interferon or the combination of the two latter drugs does not seem to significantly affect the mortality, development of respiratory insufficiency or length of hospital stay 30.
- In the results of the RECOVERY trial 31, dexamethasone reduced deaths in both ventilated patients and patients receiving oxygen only. Dexamethasone was not beneficial in patients who did not require respiratory support.
- Chloroquine and hydroxychloroquine seem to be of no benefit in the treatment or prophylaxis of the infection 32 33, and, according to the results of a meta-analysis that has not undergone peer-review yet, they do not reduce mortality 34.
- Results concerning oral ivermectin for the treatment of COVID-19 infection are uncertain, and, for the time being, the drug should not be used outside randomized controlled trials [18].
- Promising preliminary results have been obtained with the antiviral drug molnupiravir in the treatment of early COVID-19 infection [19].
- Also treatment using plasma of patients who have recovered from COVID-19 is being investigated 35.
- See also summaries produced by EBSCO concerning research on three COVID-19 drugs: hydroxychloroquine , remdesivir and dexamethasone 36.

Other guidelines

- Patient management guidance by the WHO, see 37 and the document Therapeutics and COVID-19: living guideline 38.
- Patient management guidance by the CDC, see 39.

COVID-19 testing

- Consult national and local guidance concerning criteria applied in the local epidemiological situation. Testing criteria to be applied in different situations may be available, for example, concerning:
  - Exposed individuals
  - Social and health care units, institutes and schools
  - Medical and other care units for the elderly
  - Patients entering hospitals
  - Tracing app alerts
  - Entry to the country and travel
- See also relevant guidance from the WHO and ECDC:
  - The WHO criteria for suspected, probable and confirmed cases 40
    - Notice that the WHO criteria have been defined for the purposes of COVID-19 surveillance, and hence WHO has included the following caveat with the criteria: "Clinical and public health judgment should be used to determine the need for further investigation in patients who do not strictly meet the clinical or epidemiological criteria. Surveillance case definitions should not be used as the sole basis to guide clinical management."
  - Advice on EU level surveillance of COVID-19 by the ECDC 41.

Discontinuation of isolation and precautionary measures

- National, regional and local guidelines should be followed concerning COVID-19 patients' return to work and resuming social contacts without the risk of being infectious.

- The following table indicates principles applied in Finland, as defined by the National Institute for Health and Welfare.

COVID-19 case	Requirements for discontinuing isolation and precautionary measures
...being treated in a hospital ward	No symptoms known to occur in COVID-19 for ≥ 48 hours and at least 14 days (at maximum 20 days) have passed since symptom onset
...discharged from hospital to home	No symptoms known to occur in COVID-19 for ≥ 48 hours and at least 14 days (at maximum 20 days) have passed since symptom onset
...discharged from hospital to another care facility for further care or rehabilitation	No symptoms known to occur in COVID-19 for ≥ 48 hours and at least 14 days (at maximum 20 days) have passed since symptom onset. If the patient is transferred before 14 days have passed from the symptom onset, the hospital informs the unit providing further care about the continuation of isolation and precautionary measures.
...with mild symptoms and cared for at home	No symptoms known to occur in COVID-19 for ≥ 48 hours and at least 10 days have passed since symptom onset
...is a social or health care staff member	No symptoms known to occur in COVID-19 for ≥ 48 hours and at least 10 days have passed since symptom onset before returning to work
...is asymptomatic the whole time Notice! Asymptomatic individuals may be tested in the case of insitutional epidemics.	10 days after the sample was taken

Management of contacts of patients with coronavirus infection

- The aim is to identify individuals exposed to the infection as early as possible. Depending on the epidemiological situation and resources in each region, the contacts are identified, listed and classified as close contacts or other contacts. Among close contacts the risk of transmission is higher than among other contacts.
- A COVID-19 case becomes infectious 1–2 days before symptom onset. In mild infections, viral shedding continues for no longer than just over a week. In severe infections requiring hospital care, viral shedding lasts longer and is at its peak on the 11th day. The median incubation time of COVID-19 infection is 5–6 days, ranging from 1 to 14 days.
- An exposed person is defined as someone who has had contact with a COVID-19 case within a timeframe ranging from 48 hours before the onset of symptoms of the case (the exposed persons are identified for the two days prior to onset of symptoms) to 10 days after the onset of symptoms. See also "contact person" in 42 as well as national and local guidance.
  - If the COVID-19 case has a severe form of the disease, the aforementioned number of days after the onset of symptoms may not be long enough period. Consult local guidance concerning patients with severe COVID-19.
- If the COVID-19 case is asymptomatic, an exposed person is defined as someone who has had contact with the case within a timeframe ranging from 48 hours before the sample which led to confirmation was taken (exposed persons are identified from the 2 days prior to testing), to 10 days after the sample was taken.
- Consult local and national guidance on how to define and manage various types of contacts, including:
  - Close contacts of a COVID-19 case (high-risk exposure)
  - Quarantine and testing of close contacts
  - Close contacts not ordered to quarantine
  - Other contacts (low-risk exposure)
  - Family exposures
  - Fully vaccinated asymptomatic individuals
  - Social and health care workers
- See also advice on EU level surveillance of COVID-19 by the ECDC 41.

Prevention of infection

- Several countries have declared COVID-19 as a dangerous communicable disease, with specific consequences based on local legislation.
- Avoid epidemic areas and, in them, especially crowds of people.
- Avoid close contact with persons with COVID-19 infection.
- Use appropriate protection when dealing with a person with COVID-19. See guidance from ECDC 18, WHO 43 and local sources.
- Maintain good hand hygiene (wash primarily with soap and water).
- Views vary concerning the protective effect of face masks. Fabric masks do not protect their user very well. Surgical masks are somewhat better, and FFP2 and FFP3 masks, that must not have an outflow valve, are the best. Use of masks is compulsory in several countries in public spaces and public transport. In some countries more limited policies apply and may consist of a mixture of recommendations and/or obligations and specific locations (e.g. airports or airplanes).
- When coughing or sneezing, use appropriate technique and teach it to the patients and their close ones:
    - When coughing or sneezing, protect the mouth with a disposable handkerchief, and throw the used handkerchief immediately to garbage.
    - If there is no handkerchief, cough or sneeze into the upper part of the sleeve of clothing (not into the hands!)
- COVID-19 has affected older people disproportionally. In some countries, over 40% of COVID-19 related deaths have been linked to long-term care facilities, and in some high-income countries the share is as high as 80%. See also guidance on preventing and managing COVID-19 in long-term services by the WHO 44 and ECDC 45 46.

Vaccine and vaccination

- Vaccines are available for adults and children from the age of 12 years.
- The EU has set a target of 70% for the vaccination coverage. This will most likely not be sufficient for reaching herd immunity, but instead a coverage of at least 80% would be needed.
- Many countries have started, resources allowing, to provide a third dose of COVID-19 vaccine. These may be given first to, for example, people with immunodeficiencies, social and health care workers and those who got the two first doses at a short interval.
- The vaccines already available or under development are administered either as an injection or as nasal spray.
- The vaccines provide, at best, a protective effect exceeding 90% and the protection has been almost full against severe forms of the disease.
- In the European Union, the mRNA vaccines developed by Pfizer and BioNTech as well as by Moderna and the adenovirus vaccines developed by AstraZeneca and Johnson & Johnson have acquired marketing authorization, and the vaccinations have commenced.
- Due to the risk of rare thromboembolic complications particularly in the younger age groups, the use of adenovirus vaccines has been restricted or discontinued in some countries.
    - In Finland, younger individuals vaccinated first with an adenovirus vaccine are given the second dose using a mRNA vaccine.
- mRNA vaccines have been associated with myocarditis and pericarditis as rare adverse effects, occurring in most cases in young men 47. The cases have usually been mild.
- In addition to the aforementioned vaccines – or instead of them – other vaccines may be in use in countries outside the EU.
- According to the available, preliminary, evidence, vaccination by two different types of vaccines (adenovirus vaccine and mRNA vaccine) provides a very good protection 48.
- Find out about national plans to vaccinate people in different risk groups and the remaining population.
    - Such groups are often defined by *age* (elderly people), certain types of *health care staff* (especially those working with suspected or confirmed COVID-19 cases or their laboratory samples and those working in critical tasks/areas, such as transplantation units, cancer units, advanced emergency surgery), *need for permanent care* (inhabitants and staff of various social and health care institutes), as well as people with *diseases* that predispose to severe COVID-19 infection (such as chronic kidney, liver and pulmonary diseases, immunocompromized persons, type 2 diabetes, coronary artery disease, sleep apnoea, for example).
    - Immunization of the general public has commenced and progressed far in many countries.

- See the *COVID-19 vaccine tracker* with continuously updated graphical information on the developmental stage of various vaccines and ongoing clinical vaccine trials 49.

Pfizer-BioNTech vaccine

- mRNA vaccine tozinameran BNT162b2, product name Comirnaty
- 2 doses at a 3-week interval (longer interval, e.g. 8–12 weeks, used in some countries)
- Storage temperature -70 °C
- Over 40 000 patients were randomized to get the vaccine or placebo in a trial [13]. The number of Covid-19 cases with onset at least 7 days after the second dose in participants having received the vaccine was 8 whereas there were 162 cases among those who received placebo. The protective effect was 95% (95% credible interval, 90.3 to 97.6). The protective effect was similar in all subgroups, irrespective of the sex, ethnic background, BMI, or presence of coexisting conditions. After the first dose, 10 cases of severe infections were observed, one in the vaccine group and 9 in the placebo group. Mild adverse effects included pain at the injection site, fatigue and headache. Serious adverse events were infrequent and their incidence similar in the vaccine and placebo groups.

Moderna vaccine

- mRNA vaccine mRNA-1273, product name Spikevax
- 2 doses at a 4-week interval (longer interval, e.g. 8–12 weeks, used in some countries)
- Storage temperature -20 °C
- Evidence provided by the manufacturer 50 is based on one phase III trial, with about 30 000 participants aged 18–95 years. The efficacy after two doses was 94.1 % (95% CI 89.3%–96.8%). The protective effect was similar in all subgroups, irrespective of the sex, race, ethnicity or underlying medical conditions. Adverse effects included pain at the injection site and usually mild general symptoms. Frequency of serious adverse effects was similar (1%) in the vaccine and placebo groups.
- Use of Spikevax has been suspended in certain population groups in some countries due to myocarditis occurring as a rare adverse effect. Also Pfizer's vaccine is associated with an increased risk, but it is probably lower than that of Moderna's vaccine.

AstraZeneca vaccine

- Adenovirus vaccine AZD1222, product name Vaxzevria
- 2 doses at a 3-week interval (longer interval used in some countries)
- Can be kept in refridgerator temperature.
- Use of the vaccine has been suspended or limited in several EU countries, due to rare thromboembolic complications. Thromboses have been caused by a disturbance in the whole coagulation system, and the clinical picture has included e.g. a rare cerebral venous sinus thrombosis. The EMA has confirmed a link between the vaccine and unusual blood clots, but also confirms overall positive benefit-risk balance 51. Information on this theme may change rapidly. Find out about additional national guidance on using the vaccine and on the treatment of the related blood coagulation disorder.
- According to an unpublished study 52, the COVID-19 infection itself is associated with an almost 7-fold risk (43 per million) of cerebral venous thrombosis (CVT) compared with the risk associated to a vaccine. In this study, however, mRNA vaccine was used as a comparison (6.4 per million), not the AZ vaccine. The risk was, however, significantly higher than the risk associated with the AZ vaccine described in other sources (about 5–10 per million).
- An interim analysis of a trial group with 23 848 participants has been published, concerning 11 636 participants [14]. After two standard doses, the vaccine efficacy was 62.1% (95% CI 41.0 %–75.7 %); 27 (0.6 %) cases in the vaccine group (n=4440) vs. 71 (1.6 %) cases in the placebo group (n=4455). The efficacy was 90% in participants who received first a low dose and then a standard dose (95% CI 67.4 %–97.0 %); three cases (0.2 %) in the vaccine group (n=1367) vs. 30 cases (2.2 %) in the placebo group (n=1374). The overall efficacy across both groups was 70.4 % (95% CI 54.8 %–80.6 %); 30 cases (0.5 %) in the vaccine group (n=5807) vs. 101 cases (1.7 %) in the placebo group (n=5829). 21 days after the first vaccine dose, 10 patients had been hospitalized for COVID-19, all of them in the placebo group. Two severe cases were observed, including one death. A total of 175 severe adverse events occurred in 168 participants, 84 in the vaccine group and 91 in the control group. Three events were classified as possibly related to a vaccine.
- Some final numbers concerning the protective effect have been given to publicity, indicating a 76% protective effect, and 85% in persons over 65 years of age.

Janssen (Johnson&Johnson) vaccine

- Adenovirus vaccine JNJ-78436735
- Administered as a single dose
- Can be kept in refridgerator temperature.
- In the USA, the use was temporarily suspended, due to suspected rare thromboembolic complications. The CDC has recently recommended the use of the vaccine with some caveats, saying that its benefits outweigh the risks 53. Delivery of the vaccine to Europe has started only recently due to these concerns. The EMA has confirmed such a risk but, as in the case of the AZ vaccine, concludes that the benefits outweigh risks 54. National decisions concerning the use of the vaccine may still be pending.
- Evidence provided by the manufacturer 55 is based on a single phase III trial with about 40 000 particiants aged 18–100 years. According to an interim analysis, the vaccine provided a 66.3% protective effect at ≥14 days after vaccination and 65.5 % effect at ≥28 days. The vaccine was very effective against severe infections leading to hospitalization; ≥14 days after vaccination there were 29 such cases in the placebo group and two in the vaccine group, and at ≥28 days after vaccination none in the vaccine group and 16 in the placebo group. Adverse effects consisted mainly of mild local reactions and general symptoms. All seven deaths occurred in the placebo group.

Sputnik V vaccine

- Adenovirus vaccine, in which different adenoviruses are used as carrier in the two doses.
- 2 doses at a 3-week interval
- Can be kept in refridgerator temperature.
- No marketing authorization within the EU, but some individual Eastern European countries have ordered the vaccine and it has been used at least in Hungary. Outside the EU, several countries have ordered the vaccine.
- Some countries do not recognize the vaccine as an immunization of travellers entering the country.
- According to the interim results of a phase III trial [15], 21 977 adults were randomized into a vaccine group (n=16 501) or placebo group (n=5476). A total of 19 866 participants received two vaccine or placebo doses. At 21 days after the first dose (at the time when the second dose was given) 16 (0.1 %) of the 14 964 participants in the vaccine group and 62 (1.3 %) of the 4902 participants in the placebo group had gotten a COVID-19 infection. Hence the efficacy was 91.6 % (95% CI 85.6 %–95.2 %). Of reported adverse effects, 94% were considered mild. A total of 45 (0.3%) serious advere effects occurred in the vaccine group and 23 (0.4 %) in the placebo group. Four deaths occurred, three in the vaccine group and one in the placebo group, none of which was considered being related to the vaccine.

Immunity

- Nearly all persons with severe COVID-19 infection develop antibodies against the virus.
- The antibodies seem to prevail for at least several months after the infection 26, and according to data from Finland for at least a year (preprint in 27). It is not known, however, how effective the antibodies are in preventing a new infection.
- Having had a COVID-19 infection seems to prevent a reinfection much better in yonger persons than in the elderly. In the context of the second wave of the epidemic, the protective effect was 80% in persons below 65 years of age, and only 47% in persons over 65 years 56.
- The duration of immune response produced through vaccination, or the differences between vaccine types, are not known.
- Furthermore, it is not known whether regular revaccination is required due to viral strain variation, as is the case with influenza vaccines.

COVID-19 reinfection

- A person with an earlier positive PCR or antigen test, or with a medical certificate of an earlier COVID-19 infection, when *less than 6 months* have passed since the symptom onset of the first COVID-19 infection:
  - If the person is asymptomatic, testing is normally not performed.
  - If an asymptomatic person has been tested for some reason and the test result is positive, take into account that a positive PCR test result does not necessarily mean that infective virus is still found.

- If the person is exposed to COVID-19 infection, no quarantine order is made and voluntary quarantine is not recommended.
- If the person gets symptoms that fit a COVID-19 infection and the clinical state requires diagnostic investigations, other aetiologies than COVID-19 are primarily looked for, such as influenza and other respiratory viruses.
- If another aetiology is not found, a specialist in infectious diseases is consulted concerning the verification of a possible reinfection and the existence of a prior high-risk close contact is investigated. Additionally, the need for taking a PCR test and identifying exposed persons is considered. The Ct value of the PCR test and its change can be used to assist in the interpretation.

- A person with an earlier positive PCR or antigen test result, or with a medical certificate of an earlier COVID-19 infection, when *more than 6 months* have passed since the symptom onset of the first COVID-19 infection:
  - If the person is asymptomatic, becomes exposed or gets symptoms fitting a COVID-19 infection, measures are taken based on a case-by-case assessment by the local authority responsible for control of infectious diseases.

Long-standing symptoms ("long COVID")

- After a COVID-19 infection, some patients will develop long-lasting postinfectious symptoms, such as fatigue, headache, attention disorder, hair loss, dyspnoea, other respiratory symptoms, cardiac symptoms and joint pains.
- See separate article on Long-term symptoms of coronavirus infection (COVID-19) .
- Find out about the local organization of care for those with long-term symptoms following a COVID-19 infection.

Death investigation and certificate

- In the case of death caused by COVID-19, consult local policies and instructions concerning medicolegal requirements and practices.
- For international guidelines for certification and classification (coding) of COVID-19 as cause of death, see 25.

References

1. ECDC on COVID-2019 57
2. CDC on COVID-2019 58
3. WHO on COVID-2019 59
4. EBSCO COVID-19 Resource Centre 60 and COVID-19 Updates and Information 61
5. NIH/NLM LitCovid curated literature hub on COVID-19 62
6. Zhang L, Liu Y. Potential interventions for novel coronavirus in China: A systematic review. J Med Virol 2020;():[Epub ahead of print]. PubMed 63
7. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Preliminary Report. N Engl J Med 2020;():. PubMed
8. Boulware DR, Pullen MF, Bangdiwala AS et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. N Engl J Med 2020;383(6):517-525. PubMed
9. Kucirka L, Lauer S, Laeyendecker O. Variation in false-negative rate of reverse transcriptase polymerase chain reaction-based SARS-CoV-2 tests by time since exposure. Annals of Internal Medicine, 13 May 2020 64
10. O'Callaghan K, Blatz A, Offit P. Developing a SARS-CoV-2 Vaccine at Warp Speed. JAMA. Published online July 6, 2020. doi:10.1001/jama.2020.12190 65
11. Folegatti P, Ewer K, Aley K, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. The Lancet 20.7.2020 66
12. Lu X, Zhang L, Du H ym. SARS-CoV-2 Infection in Children. N Engl J Med 2020;382(17):1663-1665. PubMed
13. Polack FP, Thomas SJ, Kitchin N ym. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 2020;383(27):2603-2615. PubMed
14. Voysey M, Clemens SAC, Madhi SA ym. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 2021;397(10269):99-111. PubMed
15. Logunov DY, Dolzhikova IV, Shcheblyakov DV ym. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. Lancet 2021;397(10275):671-681. PubMed
16. Li Y, Tong CH, Bare LA ym. Assessment of the Association of Vitamin D Level With SARS-CoV-2 Seropositivity Among Working-Age Adults. JAMA Netw Open 2021;4(5):e2111634. PubMed
17. Lopez-Leon S, Wegman-Ostrosky T, Perelman C et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. Sci Rep 2021;11(1):16144. PubMed
18. Popp M, Stegemann M, Metzendorf MI ym. Ivermectin for preventing and treating COVID-19. Cochrane Database Syst Rev 2021;(7):CD015017. PubMed

19. Fischer W, Eron JJ, Holman W ym. Molnupiravir, an Oral Antiviral Treatment for COVID-19. medRxiv 2021;():.
    PubMed