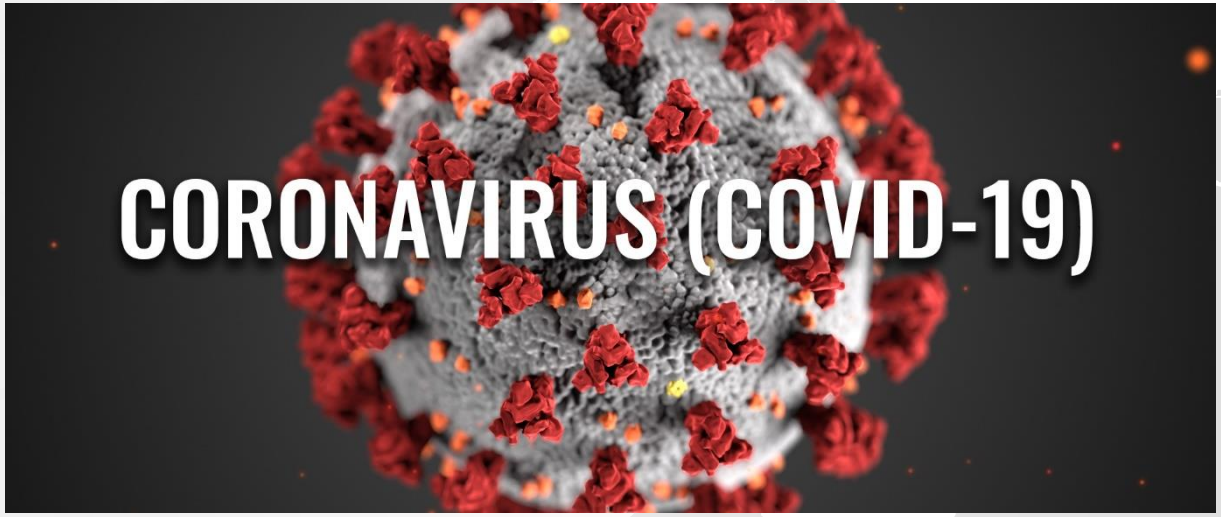


PH III Autumn 2020

mkolar@med.muni.cz

Source: website ECDC

Since 31 december 2019 and as of 01 november 2020, **46 156 540 cases** of COVID-19 (in accordance with the applied case definitions and testing strategies in the affected countries) have been reported, including **1 196 272 deaths**.

- **Cases have been reported from:**
- **Africa:** 1 787 175 cases; the five countries reporting most cases are South Africa (725 452), Morocco (219 084), Egypt (107 555), Ethiopia (96 169) and Nigeria (62 853).
- **Asia**: 13 543 771 cases; the five countries reporting most cases are India (8 184 082), Iran (612 772), Iraq (472 630), Indonesia (410 088) and Bangladesh (407 684).
- **America**: 20 684 530 cases; the five countries reporting most cases are United States (9 126 361), Brazil (5 535 605), Argentina (1 166 911), Colombia (1 074 184) and Mexico (924 962).
- **Europe**: 10 098 465 cases; the five countries reporting most cases are Russia (1 618 116), France (1 364 625), Spain (1 185 678), United Kingdom (1 011 660) and Italy (679 430).
- **Oceania**: 41 903 cases; the five countries reporting most cases are Australia (27 590), French Polynesia (7 262), Guam (4 690), New Zealand (1 603) and Papua New Guinea (589).
- **Other**: 696 cases have been reported from an international conveyance in Japan.

- **Deaths have been reported from:**
- **Africa:** 42 892 deaths; the five countries reporting most deaths are South Africa (19 276), Egypt (6 266), Morocco (3 695), Algeria (1 964) and Ethiopia (1 469).
- **Asia**: 241 008 deaths; the five countries reporting most deaths are India (122 111), Iran (34 864), Indonesia (13 869), Iraq (10 910) and Turkey (10 252).
- **America**: 642 894 deaths; the five countries reporting most deaths are United States (230 556), Brazil (159 884), Mexico (91 753), Peru (34 476) and Colombia (31 314).
- **Europe**: 268 420 deaths; the five countries reporting most deaths are United Kingdom (46 555), Italy (38 618), France (36 788), Spain (35 878) and Russia (27 990).
- **Oceania**: 1 051 deaths; the five countries reporting most deaths are Australia (907), Guam (79), French Polynesia (29), New Zealand (25) and Papua New Guinea (7).
- **Other**: 7 deaths have been reported from an international conveyance in Japan.

Case definition for coronavirus disease 2019 (COVID-19), as of 29 may 2020

Clinical criteria

Any person with at least one of the following symptoms (*Additional less specific symptoms may include headache, chills, muscle pain, fatigue, vomiting and/or diarrhoea*):

* cough
* fever
* shortness of breath
* sudden onset of anosmia, ageusia or dysgeusia

Diagnostic imaging criteria

* Radiological evidence showing lesions compatible with COVID-19

Case definition for coronavirus disease 2019 (COVID-19), as of 29 may 2020

Laboratory criteria

* Detection of SARS-CoV-2 nucleic acid in a clinical specimen

Epidemiological criteria

At least one of the following two epidemiological links:

* close contact with a confirmed COVID-19 case in the 14 days prior to onset of symptoms
* having been a resident or a staff member, in the 14 days prior to onset of symptoms, in a residential institution for vulnerable people where ongoing COVID-19 transmission has been confirmed

Case definition for coronavirus disease 2019 (COVID-19), as of 29 may 2020

Case classification

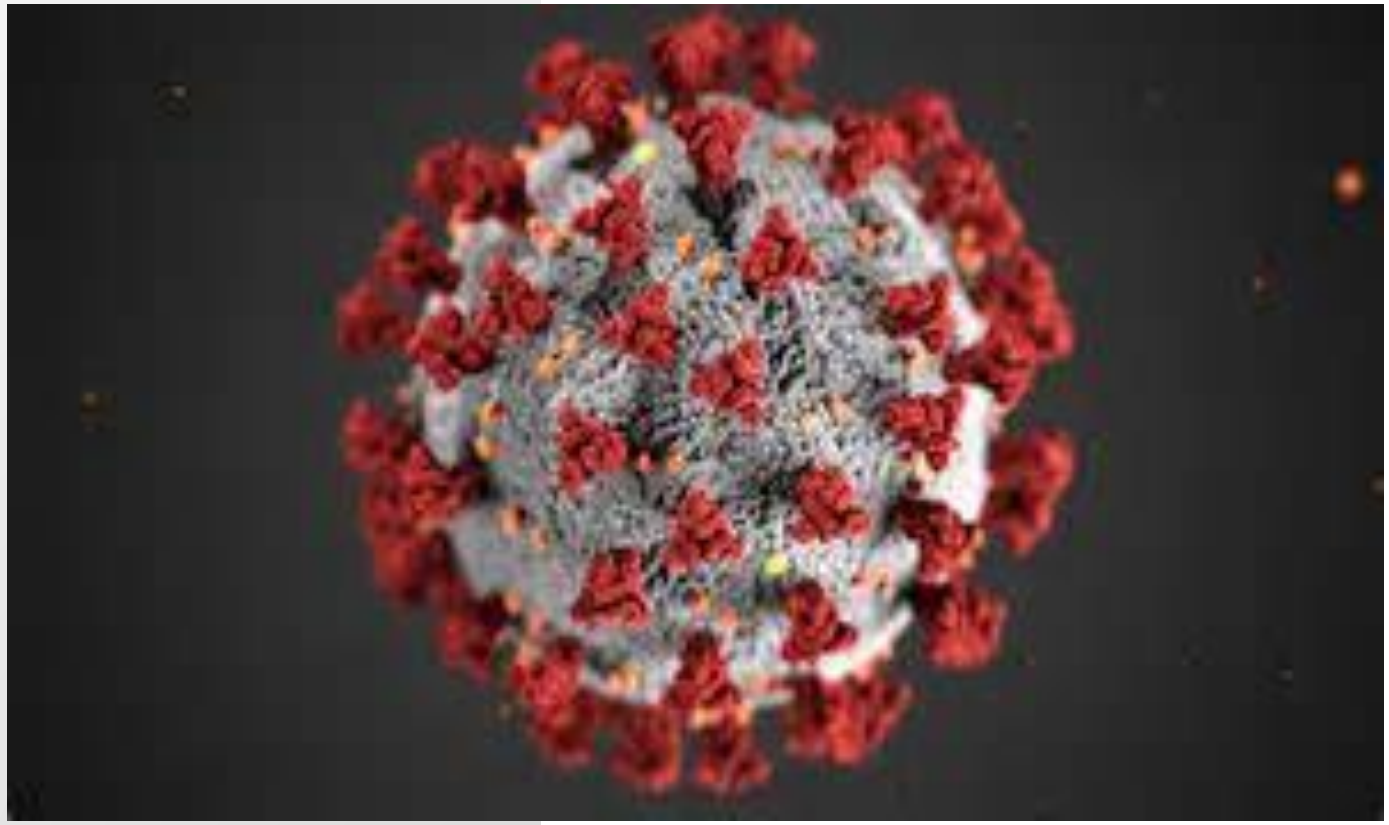
Possible case:
Any person meeting the clinical criteria

Probable case:
Any person meeting the clinical criteria with an epidemiological link or any person meeting the diagnostic criteria

Confirmed case:
Any person meeting the laboratory criteria

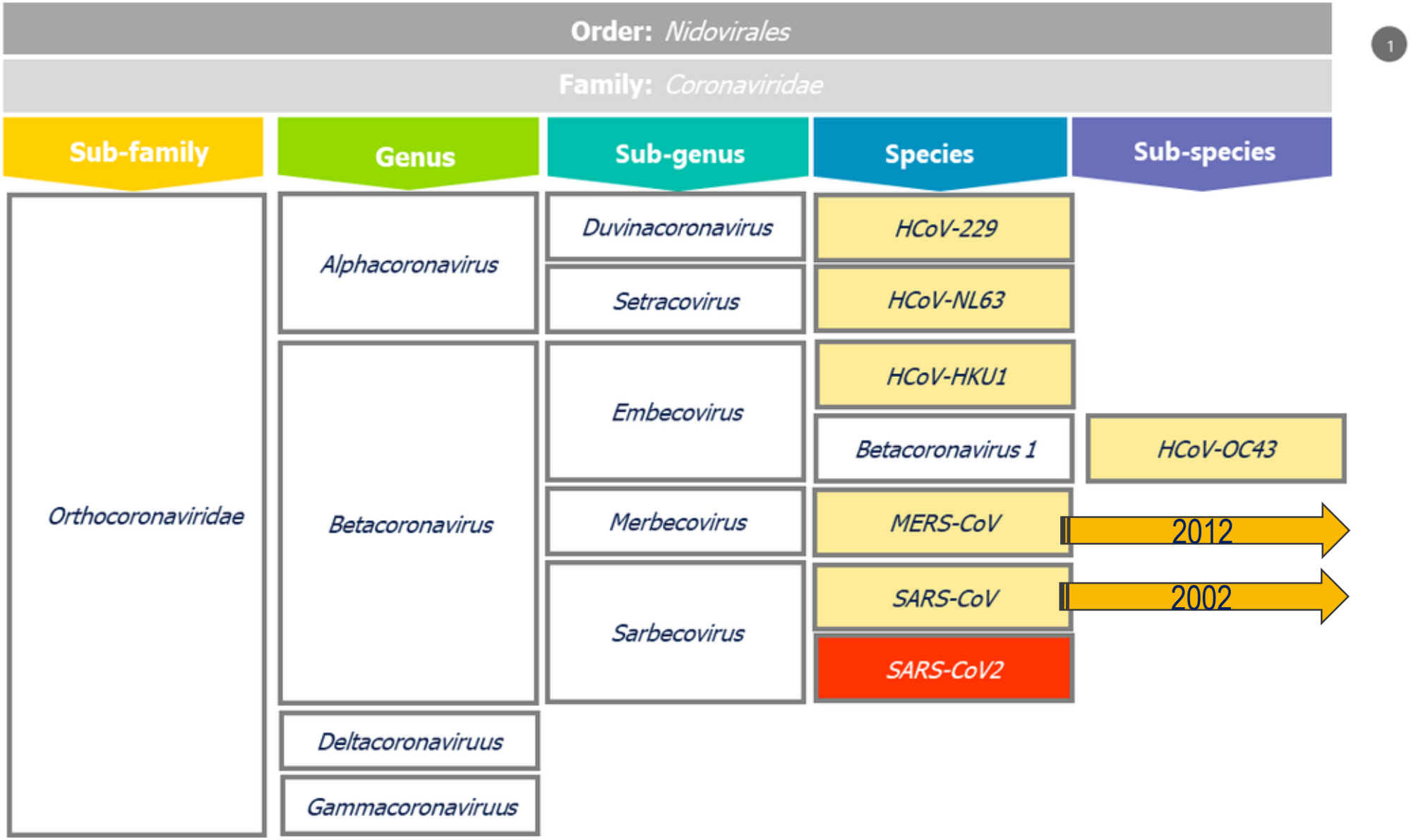
CORONAVIRUSES

With their characteristic surface, the virions have a crown-like appearance under the electron microscope, which is why the viruses are named after the Latin word corona, meaning 'crown' or 'halo‘.



CORONAVIRUSES

Coronaviruses (CoV) were identified as human pathogens in the 1960s.
They are enveloped positive stranded RNA viruses in the order of *Nidovirales:*



SARS-cov-2 virus evolution

At the end of June 2020, the GISAID EpiCoV database held more than 57 000 genome sequences (www.gisaid.org) of SARS-CoV-2.

A meta-analysis of time estimates to the last common ancestor of the virus suggested that the pandemic started sometime between 6 October and 11 December 2019.

Retrospective analysis of sewage samples from Milan and Turin showed that the virus was already present in northern Italy on 18 December 2019.
Three different time-calibrated phylogenetic analysis of closely related coronaviruses suggested that the lineage giving rise to SARS-CoV-2 diverged from the most similar known bat coronavirus between 1948 and 1982.
Bats are therefore the most likely original animal reservoir of the virus, with an intermediate animal host involved in the transmission to humans. However, the recombinant nature of coronaviruses complicates longer-term phylogenetic analysis.
Genomic evidence also indicates it is unlikely that the virus is a product of in-vitro manipulation, passaging in cell-culture, or that it is of synthetic origin.

SARS-cov-2 virus seasonality

Human coronavirus infection rates show peaks in the winter months, similar to influenza and human respiratory syncytial viruses (RSV) and are therefore, according to their seasonality, classified as winter viruses.

Low temperature and dry air impair and disrupt the integrity of the epithelial layer of the lungs, which might explain the winter seasonality of respiratory viruses.

Other factors that might contribute to transmission are increased indoor activities during the winter months, which increases susceptible host proximity.

- A cohort study of cities with substantial spread of COVID-19 from around the world examined the relationship between temperature and humidity on the epidemiology of COVID-19 – with different results
- Modelling the SARS-CoV-2 transmission dynamic based on other human coronaviruses suggests that effective reproductiveness can drop from winter to summer by 20% but can still generate substantial outbreaks (R0>1) if no control measures are in place.

Epidemiology

- Children
- Pregnant women and neonates
- Risk factors and risk groups
- Underlying health conditions among severe cases
- Elderly residents of long term care facilities and nursing homes
- Healthcare workers

Epidemiology

Children

COVID-19, like SARS and MERS, is observed less frequently in children, who tend to present milder symptoms and have a better overall outcome than adults. The most commonly reported symptoms in children are * fever and *cough. Other symptoms include gastrointestinal symptoms, sore throat/pharyngitis, shortness of breath, myalgia, rhinorrhoea/nasal congestion and headache, with varying prevalence among different studies.

Several countries affected by the COVID-19 pandemic reported cases of children who were hospitalised in intensive care units due to a rare paediatric inflammatory multisystem syndrome (PIMS) or multisystem inflammatory syndrome in children (MIS-C), characterised by a systemic disease involving persistent fever, inflammation and organ dysfunction following exposure to SARS-CoV-2.

Epidemiology

Pregnant women and neonates

Clinical manifestations in pregnant women are predominantly mild, with few reports of severe disease and fatal outcomes. According to a systematic review, the clinical presentations and severity of COVID-19 during pregnancy are similar to the disease spectrum observed in non-pregnant adults.

Pregnant women are often tested for SARS-CoV-2 infection at admission for hospital delivery. This may explain the high proportion of asymptomatic cases found among pregnant women in different countries.
Two studies from New York reported that 87.9% and 32.6% of pregnant women with positive RT-PCR results for SARS-CoV-2 at admission for delivery were asymptomatic. Data has also been reported from Sweden (7%) and China (65. 2%).
Perinatal transmission has been reported, but the exact transmission route (e.g. transplacental, transuterine or environmental) has remained unclear.
Positive RT-PCR results from placental samples have been reported, without infection in the neonates.
One case report from Iran showed positive RT-PCR results in amniotic fluid and the neonate's nasopharyngeal swabs (taken 24hrs after birth), and negative results from the mother's vaginal secretion, umbilical cord blood, and the neonate's nasopharyngeal swabs (taken immediately after birth) [41].

- One recent report demonstrated the possible transplacental transmission of SARS-CoV-2 in a neonate born to a mother infected in her last trimester and presenting with neurological symptoms [42].

Pregnant women and neonates

Epidemiology

Infants and neonates have been described as more vulnerable to severe COVID-19 than other paediatric groups in recent literature reviews, although in most cases a low mortality rate (0.006%) with favourable outcomes has been reported for this group.

- Asymptomatic infections have also been reported in infants and neonates, of whom 16% were asymptomatic in a review of 160 infants with confirmed COVID-19.
- Two studies reported increased levels of IgM and IgG antibodies against SARS-CoV-2 in neonates born to confirmed maternal cases of COVID-19.
- There are limited data to assess the role of breastfeeding in transmission.

Only one study has reported positive RT-PCR results in breast milk from a mother with mild COVID-19 [50]. Her new-born was also confirmed to be infected with COVID-19, but the actual mode of transmission remains unclear.

Epidemiology

Underlying health conditions among severe cases

Data from Italy, Spain, Sweden, Switzerland, the UK, France, the Netherlands and the US provide proportions of people with underlying health conditions among COVID-19 cases with severe disease and death.

These proportions should be seen in light of the prevalence of these conditions in the underlying populations and cannot be interpreted directly as a risk factor.

Underlying health conditions reported among patients with COVID-19 and admitted to ICU include hypertension, diabetes, cardiovascular disease, chronic respiratory disease, immune compromised status, cancer and obesity.

Elderly residents of long term care facilities and nursing homes

- A high proportion of long-term care facilities (LTCF) and nursing homes across Europe and the world have been severely affected by COVID-19. High morbidity and mortality in residents as well as high rates of staff absence due to SARS-CoV-2 infections have been observed. In several EU/EEA countries, deaths among residents have accounted for over half of all COVID-19-related deaths.

Epidemiology

Healthcare workers

Healthcare workers (HCW) are at high risk of COVID-19 infection because of more frequent exposure to COVID-19 cases and may contribute to the spread of COVID-19 in healthcare institutions.
A recent study in the United Kingdom and the US estimated that frontline healthcare workers had a 3.4 fold higher risk than people living in the general community for reporting a positive test, adjusting for the likelihood of receiving a test.
In addition, exposure to higher virus concentrations, especially from severely ill patients, may influence disease severity in HCWs.

On 6 May 2020, the International Council of Nurses reported that at least 90 000 healthcare workers have been infected with COVID-19 and more than 260 nurses have died during the pandemic.
Their data were collected from 30 countries and showed that on average 6% of confirmed cases of COVID-19 are among HCW. In the US as of 6 June 2020, it has been reported that nearly 600 frontline healthcare workers have died due to COVID-19.

Other studies however reported lower illness severity in healthcare workers, and identified **PPE use as main factor** associated with decreased infection risk. A retrospective study in 72 HCW in a large hospital in Wuhan found suboptimal hand hygiene, longer duty hours and working in a high-risk department to be associated with COVID-19.

TRANSMISSION OF COVID-19

In the scoping review published by La Rosa et al., the human coronaviruses primary transmission mode is:
person-to-person contact through respiratory droplets generated by breathing, sneezing, coughing, etc., as well as contact

- direct contact with an infected subject or
- indirect contact, through hand-mediated transfer of the virus from contaminated fomites to the mouth, nose, or eyes).

Infection is understood to be mainly transmitted via large respiratory droplets containing the SARS-CoV-2 virus.

Transmission through aerosols has also been implicated but the relative role of large droplets and aerosols is still unclear.

Indirect transmission through fomites that have been contaminated by respiratory secretions is considered possible, although, so far, transmission through fomites has not been documented.

Asymptomatic infection at time of laboratory confirmation has been reported from many settings. Some of these cases developed some symptoms at a later stage of infection.

In a recent review, the proportion of positive cases that remained asymptomatic was estimated at 16%, with a range from 6 to 41%.

A majority of these cases developed symptoms later on, with only 8.4% of the cases remaining asymptomatic throughout the follow-up period. There are also reports of asymptomatic cases with laboratory-confirmed viral shedding in respiratory and gastrointestinal samples.

- **Asymptomatic infection in children** has been described in several large case series from China, which reported 4% to 28% asymptomatic paediatric cases among cases tested based on symptoms, signs or contact tracing. A systematic review presenting data on 2 914 paediatric patients with COVID-19 from China, Spain, Iran, the Republic of Korea and the United States identified 14.9% asymptomatic cases in children. Others have reported 18% asymptomatic cases in a meta-analysis of 551 laboratory-confirmed cases in children and 16% asymptomatic cases among a European cohort of 582 children.

TRANSMISSION OF COVID-19

- Similar viral loads in asymptomatic versus symptomatic cases have been reported, indicating the potential of virus transmission from asymptomatic patients.
- Viral loads in asymptomatic patients from diagnosis to discharge tended to decrease more slowly than those in symptomatic (including pre-symptomatic) patients.
- Asymptomatic transmission (i.e. when the infector has no symptoms throughout the course of the disease), is difficult to quantify. Mathematical modelling studies (not peer-reviewed) have suggested that **asymptomatic individuals might be major drivers for the growth of the COVID-19 pandemic.**
- Pre-symptomatic transmission (i.e. when the infector develops symptoms after transmitting the virus to another person) has been reported. Exposure of secondary cases occurred 1–3 days before the source patient developed symptoms.

COVID-19

Incubation period

- Current estimates suggest a median incubation period from five to six days for COVID-19, with a range from two to up to 14 days.

Pathology and pathogenesis

- Histologic findings from the lungs include diffuse alveolar damage similar to lung injury caused by other respiratory viruses, such as MERS-CoV and influenza virus.
- A distinctive characteristic of SARS-CoV-2 infection is vascular damage, with severe endothelial injury, widespread thrombosis, microangiopathy and angiogenesis.

COVID-19

Viral shedding

Viral RNA shedding is higher at the time of symptom onset and declines after days or weeks.

Over the course of the infection, the RNA of the virus has been identified in respiratory tract specimens 1-2 days before the onset of symptoms and it can persist for up to eight days in mild cases, and for longer periods in more severe cases, peaking in the second week after infection.

Prolonged viral RNA shedding has been reported from nasopharyngeal swabs (up to 67 days among adult patients) and in faeces (more than one month after infection in paediatric patients).

- Late viral RNA clearance (≥15 days after illness onset), is associated with male sex, old age, hypertension, delayed admission to hospital, severe illness at admission, invasive mechanical ventilation, and corticosteroid treatment.

COVID-19

Viral shedding

Viral RNA has been detected in faeces, whole blood, serum, saliva, nasopharyngeal specimens, urine; ocular fluid, breast milk and in placental or foetal membrane samples. A correlation has been suggested between the isolation of viable virus and the initial viral RNA load (i.e. cycle threshold [Ct]).

- There were so far no reports of transmission of COVID-19 through substances of human origin (SoHO).

More evidence is needed to assess the importance of recent findings of viral RNA in seminal fluid and breast milk for the safety of their donation, since the infectivity of detectable RNA in breast milk and seminal fluid has not been proven.

Recommendations in the first update of the ECDC's technical document on the safety of SoHO supply in EU/EEA remain valid.

Diagnostic testing and screening for SARS-cov-2

Diagnostic specimens

Samples for diagnostic tests for SARS-CoV-2 can be taken from the upper (nasopharyngeal/oropharyngeal swabs, nasal aspirate, nasal wash or saliva) or lower respiratory tract (sputum or tracheal aspirate or bronchoalveolar lavage - BAL).

Assay types

There are three main types of detection assays relevant for COVID-19 diagnostic testing and screening, based on the target that is being detected:

- Nucleic acid tests detect the presence of viral RNA. Typically, these use an amplification step based on RT-PCR.
- Antigen tests detect the presence of a viral antigen, typically part of a surface protein.
- Antibody tests detect the presence of antibodies generated against SARS-CoV-2.

The three most used assays are enzyme-linked immunosorbent assays (ELISA), chemoluminescence assays (CLIA) and lateral flow assays (LFA).

In addition, virus neutralisation tests are used, which can specifically detect neutralising antibodies, but this is mainly used for assay validation and research. Preliminary reports on ELISA assays have shown good correlation of antibody titration results with virus-neutralising antibodies.

Apart from these main detection assays, whole genome sequencing can also be performed to determine the sequence of the SARS-CoV-2 virus in a sample, with possible quasi-species variants.

Immune responses and immunity to sars-cov-2

Immune responses

- Immune response to SARS-CoV-2 involves both cell-mediated immunity and antibody production.

- **Cell-mediated immune response**

T-cell responses against the SARS-CoV-2 spike protein have been characterised and correlate well with IgG and IgA antibody titres in COVID-19 patients, which has important implications for vaccine design and long-term immune response.

It is currently unknown whether antibody responses or T-cell responses in infected people confer protective immunity, and if so, how strong response is needed for this to occur. CD8+ T cells are the main inflammatory cells and play a vital role in virus clearance. Total lymphocytes, CD4+ T cells, CD8+ T cells, B cells, and natural killer cells showed a significant association with inflammatory status in COVID-19, especially CD8+ T cells and CD4+/CD8+ ratio. Decreased absolute numbers of T lymphocytes, CD4+ T cells, and CD8+ T cells were observed in both mild cases and severe cases, but accentuated in the severe cases. In multivariate analysis, post-treatment decrease in CD8+ T cells and B cells and increase in CD4+/CD8+ ratio were indicated as independent predictors of poor treatment outcome [5]. The expression of IFN-γ by CD4+ T cells also tends to be lower in severe cases than in moderate cases.

Immune responses and immunity to sars-cov-2

Antibody-mediated immune response and protective immunity

The detection of antibodies to SARS-CoV-2 does not indicate directly protective immunity and correlates of protection for COVID-19 have not yet been established.
Most persons infected with SARS-CoV-2 display an antibody response between day 10 and day 21 after infection.
Based on the currently available data, the IgM and IgG antibodies to SARS-CoV-2 develop between 6–15 days post disease onset. The median seroconversion time for total antibodies, IgM and then IgG were day-11, day-12 and day-14 post symptom onset, respectively.
The presence of antibodies was detected in <40% among patients within 1 week from onset, and rapidly increased to 100% (total antibodies), 94.3% (IgM) and 79.8% (IgG) from day-15 after onset.

The longevity of the antibody response is still unknown, but it is known that antibodies to other coronaviruses wane over time (range: 12 – 52 weeks from the onset of symptoms) and homologous re-infections have been shown.

SARS-CoV-2 IgM and IgG antibody levels may remain over the course of seven weeks or at least in 80% of the cases until day 49. In comparison, 90% and 50% of SARS-CoV-1 infected patients have been shown to maintain IgG antibodies for two and three years respectively. In addition, it could be important to detect nasal IgA antibodies, as the serum IgA antibodies were not raised, but IgA persisted in the nasal mucosa one year post-infection for seasonal coronavirus 229E [18].

Reinfections with all seasonal coronaviruses occur in nature, usually within three years. However, the elapsed time between infections does not mean that the protective immunity lasted for the same period of time, because the reinfection was also dependent on re-exposure. Based on the minimum infection intervals and the observed dynamics of antibody waning, the study showed that the duration of protective immunity may last 6 to 12 months.

Primary infection with SARS-CoV-2 was shown to protect rhesus macaques from subsequent challenge and casts doubts on reports that the re-positivity observed in discharged patients is due to re-infection.

Immune responses and immunity to SARS-cov-2

- **Population immunity**

- The majority of the EU/EEA Member States have still low levels of seropositivity in the general population, even without adjusting for test sensitivity and specificity.
- However, a recent study from a region Austria, which was highly affected, showed more than 40% seroprevalence of COVID-19 antibodies among its residents. Overall, with the current transmission patterns it is unlikely that population immunity levels reached by winter 2020-2021 will be sufficient for indirect protection.

Vaccines and treatment of COVID-19

- **Vaccine**

There is a large global effort to develop vaccines for protection against COVID-19 and at least 19 vaccine candidates have, as of 31 July 2020, entered clinical trials, including phase 2 and 3 trials.

Vaccines and treatment of COVID-19

- **Pharmaceutical prophylaxis and treatment**
- Potential treatments should be carefully assessed in randomised controlled trials (RCTs). There are several large-scale, multicentre trials underway that are using an appropriately robust methodology for assessment of potential therapeutics, including the WHO Solidarity Trial, several United States National Institutes of Health and national trials in several EU Member States [8,9]. Encouragement of the enrolment of patients in these clinical trials would expedite their successful and timely completion.
- Pharmaceuticals undergoing clinical trials to assess their safety and efficacy as potential treatments for COVID-19, include the antiviral nucleotide analogue remdesivir, systemic interferons and in particular interferon β-1a, and monoclonal antibodies against components of the immune system such as interleukin-6 (IL-6) and IL-4 [10].

Vaccines and treatment of COVID-19

Pharmaceutical prophylaxis and treatment

- **Dexamethasone:** On 16 June 2020, preliminary results of an open-label RCT of dexamethasone showed that it significantly reduced the 28-day mortality, particularly among critically ill COVID-19 patients receiving mechanical ventilation. There was no evidence of benefit for patients not requiring oxygen. Based on these findings, the US National Institutes of Health (NIH) recommends the administration of dexamethasone for COVID-19 patients who are either mechanically ventilated or require supplemental oxygen.
- **Remdesivir:** Preliminary results from 1 059 hospitalised COVID-19 patients enrolled in a double blind RCT showed that remdesivir was associated with shorter median recovery time compared to placebo (11 vs. 15 days).
- **Hydroxychloroquine** (HCQ): in vitro alters the uptake of the virus in cells. Conflicting results were obtained by small-scale case series and trial testing its use in combination with azithromycin in patients during the early phases of this outbreak in China and Europe.
- However, many trials such as WHO solidarity, RECOVERY found no evidence of significant benefit of HCQ for the treatment of COVID-19 and discontinued their HCQ arm .
- **Favipiravir:** A Japanese trial with 89 patients showed inconclusive results but the antiviral drug is still used in Russia.
- **Lopinavir/ritonavir**: An RCT of lopinavir/ritonavir in 199 COVID-19 patients in China did not show any statistically significant favourable effect on the clinical course or mortality when compared to standard treatment.
- Reports that **non-steroidal anti-inflammatory drugs** worsen COVID-19 through increased expression of angiotensin-converting enzyme 2 (ACE2), whose receptor is used by SARS-CoV-2 to enter the target cells, was not supported by evidence.

VACCINES AND TREATMENT OF COVID-19

- **Pharmaceutical prophylaxis and treatment**

- **Plasma therapy** (plasma with antibodies from recovered COVID-19 patients)**:**
- The administration of COVID-19 convalescent plasma (CCP) donated by individuals having recovered from the disease is a prophylactic and therapeutic option in the struggle against the pandemic.
- Initial results from various non-RCT and expanded emergency use showed no increase of adverse effects after CCP treatment and suggested that the transfusion of CCP containing a high titre of neutralising antibodies could be effective in reducing the mortality of hospitalised patients.
- More evidence from RCT is however still required to fully demonstrate the safety and efficacy of CCP, and to determine the indication, dosing and optimal CCP product characteristics. To date, several randomized controlled studies are ongoing in EU/EEA.

- The European Commission together with EU/EEA Member States, the European Blood Alliance (EBA), ECDC and other health professionals developed guidance on collection, testing, processing, storage, distribution and monitored use of convalescent plasma for the treatment of COVID-19 patients.

- The Commission also set-up an open-access EU/EEA database to collect data on CCP donations and patient outcomes following transfusions.

- On 23 August 2020, based on the scientific evidence available, the FDA issued an emergency use authorisation for investigational convalescent plasma for the treatment of COVID-19 in hospitalised patients.

Source of infection: healthcare (nosocomial) vs community transmission

The source of a COVID-19 case can be community-associated (CA-COVID-19) or healthcare-associated (HA-COVID-19), based on the number of days until the onset of symptoms, or positive laboratory test, whichever is first, after admission to a healthcare facility (on day 1). Healthcare facilities include hospitals and long-term care facilities. This is informed by current knowledge regarding the distribution of incubation periods
If required, a case-by-case evaluation of the source should take into account COVID-19 prevalence in the institution/ward, contact with known cases in the community or the healthcare facility, and any other data that plausibly indicate the source of the infection.

The case source definitions are as follows:

Community-associated COVID-19 (CA-COVID-19):

- Symptoms present on admission or with onset on day 1 or 2 after admission
- Symptom onset on days 3-7 and a strong suspicion of community transmission.

Indeterminate association (IA-COVID-19):

- Symptom onset on day 3-7 after admission, with insufficient information on the source of infection to assign to another category.

Probable healthcare-associated COVID-19 (HA-COVID-19):

- Symptoms onset on day 8-14 after admission
- Symptom onset on day 3-7 and a strong suspicion of healthcare transmission.

Definite HA-COVID-19:

- Symptom onset on day ≥14 after admission
- Cases with symptom onset within 14 days of discharge from a healthcare facility (e.g. re-admission) may be considered as community-associated, probable or definite HA-COVID-19, or to have an indeterminate association. The designation of such cases should be made after a case-by-case evaluation.
- The definition above does not apply to healthcare workers. The same categories may be used to classify the source of infection among healthcare workers, but should be based on a case-by-case assessment of the likelihood of exposure to COVID-19 cases in the healthcare setting or in the community.