Disclaimer:
This document has been written by scientists from the Epidemiology of Infectious Diseases Unit of Sciensano. Despite its recent discovery, over 4000 scientific articles on COVID-19 have already been published. The objective of this document is to summarize and interpret key information based on a comprehensive review of the literature, to help overloaded health professionals keep up to date on the subject. However, this is not a systematic review, and at the speed with which discoveries are being made, certain references included are preprint papers that have not yet been peer-reviewed. Critical appraisal of the content is, as always in our discipline, encouraged.

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Note:
Highlighted sections in this document are those that have been added since version 3 (22 April 2020):
**Pathogen**

| Virology | **Taxonomy:** COVID-19 is caused by the virus SARS-CoV-2. This virus belongs to the Coronaviridae family, in the Nidovirales order. The subgroups of the coronavirus family are alpha (α), beta (β), gamma (γ), and delta (δ) coronavirus. The four ‘common human coronaviruses’ are 229E (α coronavirus), NL63 (α coronavirus), OC43 (β coronavirus) and HKU1 (β coronavirus).

SARS-CoV-2 is a β-coronavirus. β-coronaviruses also include SARS-CoV and MERS-CoV, other acute-lung-injury causing coronaviruses of zoonotic origin. SARS-CoV-2 is most closely related to SARS-CoV, sharing roughly 80% identity at a nucleotide level (1).

**Structure:** Coronaviruses are minute (65-125nm in diameter) encapsulated viruses with a crown-like appearance under an electron microscope, due to the presence of spike glycoproteins on the envelope. Coronaviruses have large (26-32 kbs) single-stranded, positive-sense RNA genomes. The viral particles contain four main structural proteins. These are the spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins.

![Structure of respiratory syndrome causing human coronavirus](image)

**Cell entry and viral replication:** Viral binding to the cells occurs via the interaction of the S protein of SARS-CoV-2, via its receptor-binding domain (RBD), with Angiotensin-converting enzyme 2 (ACE2) (1). ACE2 is also the functional receptor of SARS-CoV. It is expressed on the surface of lung alveolar epithelial cells and enterocytes of the small intestine. ACE2 is also present in arterial and venous endothelial cells, and in arterial smooth muscle cells of multiple organs (3).

Following receptor binding, the virus must gain access to the host cell cytosol which, for coronaviruses, usually entails proteolytic cleavage of the S protein followed by the fusion of the viral and cellular membranes (3). Recent SARS-CoV-2 data indicate that the priming of its S protein for membrane fusion involves the protease TMPRSS2 (4). Fusion ultimately results in the release of the viral RNA genome into the cell cytoplasm. Based on knowledge from SARS-CoV and other coronaviruses, the next steps leading to viral replication would involve viral RNA translation, assembly of viral replicase transcription complexes, viral RNA synthesis, assembly of virions within the endoplasmic reticulum–golgi intermediate compartment, and transport of these to the cell surface inside vesicles. The newly formed infectious virions are then released from the host cell by exocytosis (3).

**Reservoir** Like for previous invasive coronaviruses, such as SARS-or MERS-Cov, SARS-CoV-2 is believed to have a zoonotic origin and to result from a cross-species transmission.

Whole genome sequencing has shown that SARS-CoV-2 is 96.2% identical to a bat coronavirus (Bat CoV RaTG13). This suggests that bat CoV and human SARS-CoV-2 might share the same ancestor, and that bats are a possible reservoir for the virus (1). Additional phylogenic studies are in favor of this hypothesis (5,6).

Nevertheless, the common epidemiological link among the initial human cluster of COVID-19 in Wuhan City (Hubei, China) was a wholesale fish and live animal market, in which bats were apparently not available for sale (7). Research is therefore ongoing to identify alternative animal reservoirs and potential intermediate hosts of SARS-CoV-2. Pangolin, snakes, and turtles have been...
identified as possible intermediate hosts based on the predicted interaction between the SARS-CoV-2 spike protein and host ACE2 (8). Various wild mammals, as well as cats and dogs, also have ACE2 configuration that is predicted to bind with SARS-CoV-2 S protein (9,10).

**Physical and chemical resistance of the virus**

In the absence of any ventilation, according to a recent study (11), SARS-CoV-2 remains viable in aerosols for 3 hours, with median half-life 1.1-1.2 hours (more information on aerosolization in section Transmission). In the same study, SARS-CoV-2 was most stable on plastic and stainless steel, with viable virus detected up to 72 hours (median half-life of 5.6 hours on steel and 6.8 hours on plastic) in the absence of any intervention (eg. no disinfection of surfaces). No viable virus could be measured after 4 hours on copper and after 24 hours on cardboard. Importantly, on all surfaces and in the air, exponential decay in virus titer was recorded over time. The finding that SARS-CoV-2 is more stable on smooth surfaces like glass, steel and plastic (several days) than on rough surfaces like paper, wood and cloth (several hours) has since been confirmed in another influential study (12).

Like other coronaviruses, SARS-CoV-2 is very stable at 4°C but sensitive to ultraviolet rays and heat (inactivated within 5’ at 70°). Furthermore, these viruses can be effectively inactivated by lipid solvents and common disinfectants including ether (75%), ethanol, chlorine-containing disinfectant, peroxycetic acid and chloroform (12,13).

Soap, which dissolves the lipid bilayer of the virus, also induces SARS-CoV-2 inactivation.

Several countries have looked at options for decontamination and re-use of personal protective equipment: decontamination of FFP2/N95 masks with H2O2 vapor in the Netherlands (14) and the USA (15) and using dry heat (30’ at 65-70°C) in Germany (16). WHO does not recommend this, but their guidance on rational use of Personal Protective Equipment (PPE) provides a practical overview of studies that have been conducted on the topic (17).

**Prevention**

<table>
<thead>
<tr>
<th>General public</th>
<th>General public For the general public, handwashing and social distancing measures are recommended to protect oneself. Keeping a distance of at least 1m means that droplets from a normally breathing person will not reach you (18).</th>
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<tr>
<td>Cloth masks</td>
<td>The possibility of asymptomatic or pre-symptomatic transmission (see lower) has fueled the debate on whether face masks should be universally recommended, not to protect the wearer but mainly to prevent spread from asymptomatic individuals. Droplets are emitted not only when coughing or sneezing, but also when breathing or speaking, though these droplets differ in size (19). A recent article investigated the protective effect of wearing a medical mask in 243 participants with a respiratory infection (‘common cold’, including non-SARS-coronaviruses) and reported that viral RNA was also detected in a small number of participants who did not cough at all during the 30-minute exhaled breath collection, suggesting transmission is possible from individuals with no obvious signs or symptoms. However, they also note that ‘the majority of participants did not shed detectable virus in aerosols or droplets. For those who did shed, viral load in both tended to be low, implying that prolonged close contact would be required for transmission’. Modeling data for Influenza suggest that population-wide use of masks could importantly reduce spread of the virus (20–22). The filtration capacity of home-made mask is lower than that of medical/surgical masks, but they do offer outward protection, despite imperfect fit or adherence (23–27). WHO, after reviewing all the evidence, still recommended against the use of community masks on April 6th, pointing out the importance of other measures like social distancing, cough and hand hygiene (28). ECDC lists a number of potential risks and benefits without either recommending or discouraging the use (29). On the other hand, important health authorities like CDC and Robert Koch Institute are now advising wearing of home-made masks for the population, in addition to social distancing measures and strict hand hygiene (30,31) whilst acknowledging the absence of compelling evidence. Likewise, both in scientific and in popular literature, several experts have insisted on the universal use of masks to be included in guidelines (32–35). A review of the evidence compiled on April 10th by a consortium of</td>
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scientists not only concluded that there is evidence on the efficiency of cloth masks but also that, based on experience with other preventive measures, the claim that their use would lead to increased risk behavior and less observance of other measures is unfounded (34).

### Personal Protective Equipment

**Health care workers**

In Belgium, for health care workers coming into close contact with possible or confirmed cases of COVID-19 (<1,5m) the use of a surgical mask, gown, gloves, and goggles or faceshield is recommended. This is in line with recommendations of the WHO (36). During the SARS epidemic, adherence to these precautions was found to be effective to avoid infection in health care workers. The effect was largest for hand hygiene and use of masks (37).

**Surgical Masks vs. FFP2**

Different health care authorities have issued different advice on the recommended PPE (38), which has led to confusion. Different types of masks exist: surgical masks or the more advanced ‘respirators’ like FFP2/3 (standard used in the EU) or N95 (standard used in the US). FFP2 masks sometimes come with an outlet valve, in which case they will only protect the individual wearing it but should never be given to a possible patient, as it will not protect the environment.

In the above-mentioned trial during the SARS epidemic (37), no difference in protection of health care workers (HCWs) was found between the use of N95 masks or surgical masks. Randomized control trials (RCTs) in Canada and the US (the larger of which included 2826 participants) have evaluated the use of surgical masks versus N95/FFP2 masks in prevention of respiratory diseases in health care workers and have found them to be both equally effective (39,40). This conclusion was confirmed by a meta-analysis including six RCTs published very recently (13 March 2020) by the Chinese Cochrane Center (41). Some specific evidence for SARS-CoV-2 is also available from South Korea, where 41 health care workers were unknowingly exposed to aerosol-generating procedures on a COVID-19 patient. Of the thirty-five HCWs (85%) that wore a surgical mask, none were infected. Reassuringly, the WHO China Joint Mission Report notes that most infected HCWs in China were infected within their households (42).

Therefore, surgical masks seem to suffice for most HCWs and N95/FFP2 masks should be used preferentially for aerosol-generating procedures, such as endotracheal intubation and cardiopulmonary resuscitation (43).

**Aerosol-generating procedures**

Aerosols differ from droplets because of their smaller size, which allows them to stay suspended in the air for much longer. The evidence, the best of which comes from studies of SARS-CoV, suggests a consistent association between pathogen transmission and tracheal intubation (44). In addition, a few studies reported an increased risk of SARS-CoV infection associated with tracheotomy, noninvasive ventilation, and manual ventilation before intubation. However, because these findings were identified from only a few studies of very low quality, interpretation and practical application are difficult (45). No other procedures were found to be significantly associated with an increased risk of acute respiratory infection transmission. On theoretical grounds however, the following procedures should be considered aerosol-generating procedures: (38,46)

- Intubation, extubation and related procedures
- Prone positioning, disconnecting the patient from the ventilator
- Administration of medication via nebulization (to be replaced by use of spacers)
- Tracheotomy/tracheostomy procedures
- Manual ventilation
- Open suctioning
- Bronchoscopy
- Non-invasive ventilation (NIV) e.g. Bi-level positive airway pressure (BiPAP) and Continuous positive airway pressure ventilation (CPAP)
- Some dental procedures (e.g. high-speed drilling).

Different authorities list different procedures. Some authors argue that certain other procedures/equipment may generate an aerosol from material other than patient secretions and
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that it is unclear if they represent a significant infectious risk. Procedures in this category include administration of pressurized humidified oxygen and administration of medication via nebulization (43,44,46).

Vaccine
There is currently no vaccine available against SARS-CoV-2 infection. Considerable efforts are being deployed internationally to develop a vaccine. According to a recent review, there are currently 78 confirmed vaccine candidates. Various vaccine technology platforms are being evaluated, including "nucleic acid (DNA and RNA), virus-like particle, peptide, viral vector (replicating and non-replicating), recombinant protein, live attenuated virus and inactivated virus approaches” (47).

Ventilation
When performing aerosol-generating procedures, WHO recommends 6-12 air changes/h (45). Concerns have been raised about the pertinence of the recommended 1,5m distance, in view of possible long-range airborne transmission (see ‘transmission’). Additionally, research from MIT showed that a person sneezing emits a multiphase turbulent gas cloud containing droplets of all sizes which travel for up to 7-8m (48). Whilst probably of limited impact outdoors, it seems therefore important to provide an adequate ventilation of rooms to reduce the risk of transmission. Two-and-a-half air changes are required to eliminate 90% of airborne contaminants (49). Opening doors and windows can generate around 5-17 air changes per hour (50,51).

When using air conditioning, it is advisable to use the ‘extraction mode’ and avoid recirculation of air (52). A cluster was described in a Chinese restaurant with closed windows, where the air current from the air conditioning presumably facilitated the infection of people sitting at 2 neighboring tables (upto +- 5m).

Clinical Aspects

Transmission
Evidence indicates that SARS-CoV-2 is transmitted from human to human by infectious droplets (53). Based on experiences with previous outbreaks of SARS and on experimental evidence, other routes of transmission are also debated. One possible additional route is the long-range airborne route. For SARS, both evidence from modelling studies (54,55) and positive air samples from a patient’s room (56) indicated a potential for airborne transmission. This raises concerns about a similar airborne transmission potential for the 2019 novel coronavirus, SARS-CoV-2. In one experiment, SARS-CoV-2 was purposefully aerosolized and kept in a closed container in optimal circumstances (11). After 3h, viable virus could still be detected. The amount of infective virus was however halved each 1,1h. Whilst worrying, these findings need to be interpreted with caution, as these experimental circumstances are not representative of real-life circumstances. Natural ventilation, for instance, has been shown to dilute aerosols (51). In Singapore, researchers sampled the air and several surfaces of the isolation room of three patients with SARS-CoV-2 (57). The virus could be found on many surfaces like door handles and light switches, but all air samples were negative. Moreover, all samples (both from air and surfaces) taken after routine cleaning were negative. Unpublished data did detect SARS-CoV-2 in air samples of patients in negative pressure rooms, but the implication is unclear as no viral activity could be shown in cell cultures (58). Likewise, viral RNA was detected in air samples from both the COVID-19 ICU ward and a COVID-19 general ward of a Chinese hospital, but infectiousness remains unknown. (59)

SARS-CoV-2 viral RNA has been found in many other samples than nasopharyngeal swabs such as faeces, blood and (very rarely) urine (60–62). Especially in faeces, viral RNA seems to be present later and persists longer than in samples from the upper respiratory tract (63). Faeco-oral transmission therefore needs to be considered. Importantly though, presence of viral RNA does not equal infectious potential. Data is currently limited, but a German team did detailed analyses on samples from 9 patients. They reported that infectious virus (as proven by viral culture) was readily isolated from throat- and lung-derived samples but not from stool samples, despite high viral load. Moreover, no infectious virus could be isolated from the various sample sites after day 8 of symptom onset, despite ongoing high viral loads (64). Only one study (published in Chinese) has cultured SARS-CoV-2 from a stool sample, and no documented faeco-oral transmission has occurred (65). Finally, although in limited number, PCR-positive conjunctival swabs have been reported in COVID-19
patients, with or without ocular symptoms (eg. conjunctivitis), indicating a potential route of transmission via the ocular mucosa (66). For this reason, ocular protection (goggles, face shield) is part of the standard PPE for health care workers when in close contact with cases (cfr section PPE).

That direct contact, rather than airborne spread, is the main transmission route, seems to be supported by evidence from contact tracing. Pre-print data from 391 cases from Shenzhen and 1286 close contacts show 6x higher odds of infection in household contacts (secondary attack rate 15%) than in other close contacts (67). The CDC also investigated 445 close contacts of 10 travel-related cases and reported two infections in household members (secondary attack rate 10.5%) and zero in other contacts (68).

The basic reproductive number, the so-called R0, of the virus is thought to be between 2-4 (69) meaning that in a fully susceptible population, one infected individual will on average infect 2-4 others in the absence of control measures. To control an epidemic, the effective reproductive number needs to be less than one. The effective reproductive number is influenced by measures that are put in action like social distancing, quarantining and contact tracing.

For information on SARS-CoV-2 and blood donations, cfr section on virus and blood donations in ECDC document ‘Disease background of COVID-19’

Incubation period

The mean incubation period (the period between infection and onset of symptoms) is about 4-6 days with about 95% of individuals developing symptoms within 14 days from infection (70–72).

Analysis of 90 pairs of confirmed cases in Italy, showed a mean serial interval (the period between onset of symptoms in the primary case and onset of symptoms in the secondary case) of 6.6 days. They estimate that 95% of cases will develop symptoms within 16.1 days of symptom onset in their infector (73).

Contagious period

Beginning of contagious period: Many factors remain unknown. Viral load in the upper respiratory tract is highest immediately one day before and the days immediately after onset of symptoms (74–77). Evidence has been accumulating on pre-symptomatic transmission (76,78–82). The strongest evidence comes from detailed analysis of cases and contacts in Singapore, where 7 clusters with likely pre-symptomatic transmission were identified (83). Cases in these clusters accounted for 6.4% of total locally acquired cases. Similarly, early data from Lombardy (Italy) show only a limited number of asymptomatic cases identified through contact tracing, suggesting a minor role for asymptomatic individuals in the overall spread of infection (73). In contrast, in a modelling study, pre-symptomatic transmission was deemed likely based on a shorter serial interval (the period between onset of symptoms in the first case and onset of symptoms in the second case) than the mean incubation period. In this study, pre-symptomatic transmission was thought to account for 48-62% of all transmission when containment measures were in place (84). Contact tracing guidelines from ECDC therefore consider all potential contacts of a case from 48h before symptom onset (85). Since coughing and sneezing increase the amount of droplets that are expelled, the highest transmission potential (in absence of containment measures) seems to be for symptomatic individuals.

End of contagious period: When the contagious period ends, is not very clear either. Although viral loads drop after the first week, prolonged shedding has been described (up to 37 days) (61,86). Viral shedding does however not equate with contagiousness, and no infectious virus has been isolated after D8 after symptom onset (64), see also topic ‘transmission’. Also, several studies report positive tests after initial negative results (87,88), possibly due to false negative RT-PCR result or prolonged viral clearance rather than recurrence of infection (88). In a case-ascertained study from Taiwan of 100 COVID-19 cases and 2761 close-contacts, secondary attack rates was significantly higher among contacts whose exposure to the index case started within 5 days of symptom onset compared with those exposed later (zero secondary cases identified in the 852 contacts exposed to index case after day 6 of symptom onset) (78).

Asymptomatic infections

Asymptomatic infection at the time of laboratory confirmation has been reported from many settings (73,89–94). A large proportion of these cases developed some symptoms at a later stage of infection, although there are reports of cases remaining asymptomatic throughout the whole duration of laboratory and clinical monitoring (91–94). Overall, major uncertainties remain with regard to the
influence of asymptomatic infections on the overall transmission dynamics of the pandemic. In clinical studies with broad testing approaches (testing of symptomatic and asymptomatic), the weight of asymptomatic cases varies according to the setting, possibly due to a different age distribution of the study population. In the Diamond Princess Cruise ship, the estimated asymptomatic proportion was 17.9% (95% credible interval (CrI): 15.5-20.2%) (90); according to data from Shenzhen (China), 20% of PCR-positive close contacts were asymptomatic at the time of testing (67); in Japanese nationals evacuated from Wuhan on chartered flights, the percentage of asymptomatic cases was estimated at 30.8% (95% confidence interval (CI): 7.7%, 53.8%) (91). In Iceland, citizens were invited for testing regardless of symptoms. Of all people with positive test results, 43% were asymptomatic (95). The actual number of asymptomatic infections might be even higher since it seemed that symptomatic persons were more likely to respond to the invitation. That young and healthy people have more asymptomatic infections seems to be confirmed by unpublished data from a US Navy ship where 60% of 600 positive tests were in asymptomatic people.(96) However, it is unknown which proportion of these ‘asymptomatics’ would go on to later develop symptoms. In New York, all 215 women admitted to an obstetric unit were screened for SARS-CoV-2. Of all 33 women who tested positive, only four (12%) presented with symptoms, and three more (9%) developed symptoms during admission (97). Even in an elderly population, the proportion of asymptomatic infections might be higher than previously assumed: data from a nursing home in the US showed that half of all residents who tested positive did not have any symptoms (although difficult to ascertain in a cognitively-impaired population) and viral loads were comparable for symptomatic and asymptomatic residents (98) Similar viral loads in symptomatic vs. asymptomatic cases have also been reported in several other studies (73,74).

### Symptoms

The most frequent symptoms are fever, cough, and shortness of breath. In the analysis of >1000 hospitalized patients from China, 44% initially presented with fever (although 89% developed fever at some point during hospitalization) and 68% with cough (72). Other symptoms include fatigue (23%), myalgia (15%), and gastrointestinal symptoms (+-8%) (86). Shortness of breath often develops around day 7 after symptom onset.

As with other systemic viral infections, a large spectrum of possible clinical manifestations are being reported in COVID-19 patients, including symptoms and signs of neurological involvement (eg. chemosensory dysfunction, viral encephalitis etc), cardiac disease (eg. myocarditis) and cutaneous lesions (eg. erythematosus rash, widespread urticaria) (99–102). Chemosensory dysfunction, such as anosmia and dysgeusia (either isolated or in combination with other symptoms) are increasingly reported. Recently, several studies, including a European multicenter study reported a high prevalence of both olfactory and gustatory dysfunctions in the clinical presentation of mild-to-moderate forms of COVID-19 (103,104). Notably, anosmia has been reported after infection with other respiratory or coronaviruses (105).

Data from more than 72,000 cases from China classified cases as mild (81%), severe (14%), or critical (5%) (106). Mild presentations include mild pneumonia. The actual number of mild presentations is probably higher, as due to detection policies this dataset contains only 1,2% asymptomatic cases, much lower than is currently thought to be the case (cfr. supra).

### Complications and mortality

As aforementioned, according to the Chinese experience, severe cases and critical cases occur in approximately 14% and 5% respectively. These cases present with severe pneumonia, septic shock, and acute respiratory distress syndrome (ARDS). The critically ill patients requiring intensive care management, as with other severe viral pneumonias, present a large spectrum of complications in addition to ARDS (eg. acute cardiac injury, acute renal injury, acro-ischaeemia, disseminated intravascular complications, bacterial or fungal superinfections etc.) (107,108).

Evidence is emerging that COVID-19 is associated with an increased risk of thromboembolic disease (109,110) and a high rate of cardiovascular complications (102). A high incidence rate of severe pulmonary embolism, exceeding 10%, in COVID-19 ICU (intensive care unit) patients has been observed (pre-published data, Strasbourg, Lille, Grenoble, and Cremona-Italy) (111). In a double-center study in the Netherlands, a 31% incidence of thrombotic complications in ICU patients with COVID-19 infections is reported (112).
Reported case-fatality rates (CFR) depend on screening policies (which impact the number of asymptomatic/mild cases recorded and hence increase the denominator), clinical management factors (like availability of intensive care), and the underlying population (e.g. age, comorbidities). In early stages of the outbreak, CFR was 17% in China but decreased to 0.7% (42). In Wuhan, in admitted patients, mortality reached 25% in the middle of the epidemic (86). On March 22, the CFR in the oldest age group (>80y) in Italy was 23% (113). Similarly high death rates are recorded in those requiring intensive care: in a large retrospective case series on COVID-19 confirmed patients admitted to intensive care units (Lombardy, Italy), mortality reached 26% (114).

**Immunopathogenesis**

**Pathogenesis**

The exact pathogenesis of COVID-19 remains to be elucidated. Reviews on the topic infer from initial data on COVID-19 and knowledge from closely-related infections, such as SARS-CoV and Mers-CoV. Here we focus on the possible mechanisms involved in the development of severe disease.

The virus presumably enters the body through the mucous membranes, principally the nasal and larynx mucosa, and enters the lungs through the respiratory tract. In a nonhuman primate model (cynomolgus macaque), SARS-CoV-2 replicates efficiently in respiratory epithelial cells throughout the respiratory tract (nasal cavity, bronchi, bronchioles, and alveoli), with replication in lower respiratory tract fitting with the development of lung disease (115). In this animal model, whereas MERS-CoV primarily infects type II pneumocytes, both SARS-CoV and SARS-CoV-2 also infect type I pneumocytes. Injury to type I pneumocytes can result in pulmonary edema, and formation of hyaline membranes (115).

Persistence of high viral loads has been associated with disease severity (116). In addition to a direct viral cytopathic effect, it is likely that hyper-immune responses to the virus contribute to the development of complicated COVID-19 and end organ damage, in particular to acute respiratory distress syndrome (ARDS). In SARS-CoV and MERS-CoV, a delayed release of interferons (IFNs) is observed in the early stages of infection, hindering the body’s antiviral response. This is followed by a rapid increase in cytokines and chemokines, a "cytokine storm", that attracts many inflammatory cells, such as neutrophils and monocytes to the lungs. The excessive infiltration of the lung tissue by inflammatory cells results in lung injury (117). A growing body of evidence indicates a similar disease pathogenesis in SARS-CoV-2 infection. Immune injury was described in the post-mortem biopsies of a patient deceased from COVID-19 related-ARDS, in which interstitial mononuclear inflammatory infiltrates, dominated by lymphocytes, were found in both lungs (118). In addition, in a study by Huang et al, multiple cytokines and chemokines were found at higher concentrations in hospitalized COVID-19 patients than in healthy adults, among which IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNFα were significantly higher in intensive care unit (ICU) patients than non-ICU patients (119).

Another study reported that the increased expression of IL2R and IL6 in serum appeared to predict the severity and prognosis of patients with COVID-19 (120). A hyper-immune response in COVID-19 is also supported by the finding that peripheral CD4 and CD8 T-cells, although being substantially reduced in severe COVID-19, display characteristics of over-activation (increase in HLA-DR/CD38 expression, increase in highly pro-inflammatory Th17, and a high cytotoxicity of CD8 T-cells) (118).

Post-mortem autopsies of 3 patients have revealed the presence of viral elements within endothelial cells and an accumulation of inflammatory cells, with evidence of endothelial and inflammatory cell death. SARS-CoV-2 infection may therefore induce endotheliitis in several organs as a direct consequence of viral involvement and of the host inflammatory response, potentially explaining the systemic impaired microcirculatory function found in different vascular beds of patients with COVID-19 (121).

A hypercoagulable state in severe COVID-19 patients associated with poorer outcome is suspected. High levels of pro-inflammatory markers, fibrinogen, and fibrinogen/fibrin degradation products (including D-dimers), prolonged prothrombin times and disseminated intravascular coagulation are described in cases of COVID-19 (86,107,122,123). In-hospital death has been associated with d-dimer concentrations greater than 1 μg/mL (odds ratio 18.42, 95% CI 2.64-128.55; p=0.0033) on admission (86). In a single center study of 183 hospitalized patients, non-survivors (n=21) revealed significantly
higher D-dimer and fibrinogen/fibrin degradation product levels, and longer prothrombin times compared to survivors (n=162, discharged or hospitalized with stable conditions). Overt disseminated intravascular coagulation was found in 1.4% of non-survivors against 0.6% in survivors (123). Moreover, as mentioned in the section “complications and mortality”, an increased risk of thromboembolic disease and a high rate of cardiovascular complications is observed in severe COVID-19 patients.

In addition, the activation of complement pathways may play a role in severe disease. In a recent study, complement-mediated microvascular injury was reported in lung and/or skin biopsies of 5 individuals with severe COVID-19. In these patients, hallmarks of classic ARDS were not prominent in lung biopsy. However, significant deposits of complement components were found in the microvasculature of the lung and/or the skin (purpuric lesions) that were consistent with systemic activation of the alternative and lectin-based complement pathways (124).

An additional mechanism of disease pathogenesis hypothesized by several authors is antibody-dependent enhancement (ADE) (125,126). ADE is a well described phenomenon found with several viral infections, where non-neutralizing antibodies have the potential to mediate enhancement of viral infection or disease, by facilitating virus entry into host cells and increasing infectivity. Briefly, virion-antibody complexes are formed that can infect immune cells (eg. monocytes, macrophages, neutrophils, NK cells or B-cell lymphocytes) via Fc or complement receptors, i.e. independently of a virus specific receptor. ADE can elicit sustained inflammation, lymphopenia, and/or a cytokine storm. The phenomenon requires prior exposure to similar antigenic epitopes (eg. circulating in local viruses). ADE has been reported in SARS-CoV-2 (127). Whether ADE is involved or not in SARS-CoV-2 disease pathogenesis is still unknown.

Protective immunity & re-infection

A specific humoral response is mounted in a majority of persons after symptomatic COVID-19 infection, as shown by high antibody seroconversion rates (cfr. section on serology). Data on seroconversion rates in pauci- or asymptomatic patients remain scarce, and the duration of persistence of circulating antibodies against SARS-CoV-2 is not yet known. Whether the presence of SARS-CoV-2 specific antibodies confers immunity to subsequent infection (carriage or disease) in humans also remains to be studied.

The possibility of early re-infection (or viral re-activation?) was raised following several press-releases on suspected cases of re-infection in China and South Korea. In published literature, re-positivity of PCR on respiratory samples after clinical recovery and/or a series of negative samples are described (87,88), however, false negative RT-PCR result or prolonged viral clearance rather than recurrence of infection are suspected (88). In a rhesus-macaque COVID-19 model, primary infection appeared to protect against early reinfection. After an initial challenge with SARS-CoV-2 resulting in mild to moderate disease, 4 monkeys were re-challenged upon recovery with an identical strain (28 days after initial challenge). No detectable viral dissemination, clinical manifestations nor histopathological changes were found after this second challenge (128). In these macaques, the titers of neutralizing antibodies linearly increased after the primary infection. Authors concluded that this enhanced neutralizing antibody response might contribute to the protection of the monkeys from reinfection by SARS-CoV-2.

Virus-specific neutralizing antibodies (Nabs) are antibodies that not only bind to a virus, but block viral infection of the host cell. Highly effective Nabs protect against future infections and are considered as good correlates of immunity and protection after either infection or vaccination. In a study analyzing plasma samples collected from 175 recovered COVID-19 patients after mild to moderate disease, Nabs were found in a majority of patients between day 10 and 15 of disease onset. Notably, 30% of the recovered patients generated very low titers, and Nabs could not be detected in 10 patients. Titers correlated with markers of severity (older age, low lymphocyte count and high CRP on admission) (129).

Because of the gaps of knowledge within this field, experience from related infections is important. With the closely related SARS-CoV-1, antibodies (including Nabs) have been shown to persist for 1 to 2 years, possibly longer (130,131). In MERS-CoV patients, specific IgG antibodies were shown to persist at least one year in patients with severe disease (n=5) and in 2 out of 6 patients with mild disease (132). However, protection against re-infection, due to the limited duration or spread of these epidemics, is unknown. In contrast, antibody titers after infection with common coronaviruses (229E, NL63, OC43,
HKU1) rapidly return to baseline levels, within 4 to 12 months. Reinfection with these coronaviruses are frequent, and are possible within the same a year. The weak pathogenicity of these seasonal coronaviruses, with possibly an immune response restricted to the upper respiratory tract mucosa, may be the reason for short-lived immunity (133).

The potential role of specific T-lymphocyte immunity in protection from re-infection by SARS-CoV-2 also warrants investigation. In SARS-CoV-1 recovered patients, specific memory T cells have been shown to persist in the peripheral blood of patients, particularly after severe infection (134).

**Diagnosis**

**Overview**

COVID-19 is confirmed by the identification of the SARS-CoV-2 RNA in biological samples. In addition, clinical presentation (cfr. Clinical aspects), biological markers, and imagery contribute to the diagnosis of COVID-19.

Nevertheless, there is currently no perfect ‘gold standard test’ for the diagnosis of COVID-19 to which diagnostic tools can be compared to. Reported sensitivities and specificities should be considered with caution. Moreover, the positive and negative predictive values of the test will depend on the prevalence of the virus and therefore on the stage of the epidemic. In addition, timing of testing with regards to symptom onset is an important factor to consider when comparing the diagnostic tools. Indeed, viral loads in the upper respiratory tract are highest in the day prior and initial days of symptom onset while Chest CT and serology appear to have increased performances later in disease. Knowing the advantages and limitations of each tool is essential, to use tests and interpret results adequately.

**Laboratory findings**

In a retrospective cohort study including 191 PCR-confirmed adult inpatients (Wuhan, China), 40% had lymphopenia (< 0.8 x10⁹/L), 67% had elevated Lactate deshydrogenase (LDH > 245 U/L), and 80% had >300 µg/L of serum ferritin on hospital admission (86).

**RT-PCR**

The majority of molecular diagnostics developed for the detection of SARS-CoV-2 involve real-time RT-PCR. These assays are indicated for the qualitative detection of nucleic acid from SARS-CoV-2 on upper respiratory tract samples (eg. naso-pharyngeal specimens, oro-pharyngeal specimens) and lower respiratory tract samples (eg. bronchoalveolar lavage (BAL) specimens, endotracheal aspirates, expectorated sputum). First line testing generally involves upper respiratory tract samples, which are easier to perform and have lower viral transmission risk. Lower respiratory tract samples are reserved for selected hospitalized or ICU cases. RT-PCR have also been used on other sample types, including blood or faecal samples, but these are not used for diagnostic work-up.

**Sensitivity of RT-PCR** for the diagnosis of COVID-19 will depend on various factors, including type of specimen, timing of sampling, sampling technique, and also test kit quality.

- **Type and timing of specimen**: the overall quality of studies to accurately assess sensitivity of PCR is low: different definitions are used (eg. ‘pharyngeal’ has been used to refer to both naso-pharyngeal and oro-pharyngeal samples, ‘nasal’ for either naso-pharyngeal or anterior nares), timing of testing with regards to symptoms are not always addressed, reference used for sensitivity calculation not specified, primer used for assay not described etc. However, comparisons within studies give certain indications. Sensitivity of RT-PCR appears to be higher for lower respiratory samples than for upper respiratory tract samples (60,64,135). In a study including 213 COVID-19 cases and analyzing 866 respiratory tract samples (Shenzhen, China), in the first week of symptom onset, sputum samples showed the highest positive rate in both severe (88.9%) and mild (82.2%) cases, followed by naso-pharyngeal swabs (73.3%, 72.1%) and throat swabs (60.0%, 61.3%). BAL showed 100% sensitivity in severe cases in days 8 to 14 of onset. In this time period, positive rate of sputum remained higher than that of naso-pharyngeal swabs, and positive rates of pharyngeal samples dropped to 50% in severe and 29.6% in mild cases. This is not unexpected as viral load in the upper respiratory tract is highest one day before and the days immediately after onset of symptoms (74–77). RT-PCR may remain positive longer in lower respiratory samples (64,135). In a prospective cohort of 67 COVID-19 pneumonia cases (Chongqing, China), median duration of SARS-CoV-2 RNA shedding was 12 days (3-38 days) in nasopharyngeal swab versus 19 days (5-37 days) in sputum. In this
study, prolonged viral shedding was also observed in severe patients compared to non-severe patients (135).

- **Sampling technique and pre-analytical precautions**: correct sample collection technique is essential to ensure best test performance and avoid false-negatives. Guidance is available in Fr and Dutch. Correct swabs (preferably flocked), transport medium (Universal Transport Medium) and transport precautions to laboratory (ideally immediately after sample collection) must be applied.

- **Test kit quality**: several studies have been published comparing SARS-CoV-2 detection assays (136,137), and assays have used different primers. Instructions for test validation in Belgium are available in Fr and Nl.

### Specificity of RT-PCR

For the diagnosis of COVID-19 is high. With the exception of SARS-CoV, no cross-reactivity is found when tested against a large panel of microorganisms including the common human coronaviruses (138). A false positive would presumably occur only in the case that a non-positive sample is contaminated by viral material during the post-sampling processing of the test.

### Chest CT

Chest Computerized Tomography (CT) has been increasingly shown to be a useful tool for the diagnosis of COVID-19. As summarized by the European Society of Radiology, the *typical radiological findings* in the early phase of the disease are bilateral ground glass opacities, with a predominantly peripheral, sub-pleural location. Crazy paving and organizing pneumonia patterns are seen at a later stage, and extensive consolidation is associated with a poor prognosis (139).

To help radiologists familiarize themselves with the CT appearance of COVID-19 infection, several online tools compiling and sharing Chest CT images of COVID-19 patients have been developed:

- https://pubs.rsna.org/2019-nCoV#images
- https://radiologyassistant.nl/chest/covid-19-corads-classification

**Chest CT appears to offer a good sensitivity** for COVID-19 diagnosis. In a large retrospective study of patients in Wuhan that underwent both Chest CT and PCR (n=1014), among the 601 patients with a positive PCR, 580 had a positive CT (97%). Positive Chest CT was also found in 380 patients that had negative PCR results, among which 147 were considered ‘highly likely’ of COVID-19 based on clinical symptoms and typical CT features with dynamic changes (obvious progression or improvement in a short time) on serial CT scans (140). Inversely, negative Chest CT in PCR positive patients has also been reported (141), indicating that a normal CT should not exclude COVID-19 infection. Notably, sensitivity of Chest CT appears to be lower in the initial days after symptom onset. In a small retrospective study, 20 out of 36 PCR-confirmed patients (56%) had normal Chest CT in the first 48h of symptom onset, whilst this percentage dropped to 9% in patients tested between days 3 to 5 (142). In Wang et al’s study on temporal changes of Chest CT in COVID-19 pneumonia (n=366), the extent of lung abnormalities on CT peaked in days 6 to 11 after symptom onset. In this study, an approximate sensitivity of 84% (95% confidence interval: 73%-92%) was estimated for illness days 0-5, against 99% (93%-100%) for days 6-11 (143). Notably, positive CT has also been described in asymptomatic and pre-symptomatic persons. In a small study of 24 asymptomatic carriers of SARS-CoV-2, identified through contact tracing, half showed typical findings on Chest CT, 5 had atypical findings and 7 had normal CT images (94). Similarly, on the “Diamond Princess cruise ship”, 41 out of 76 asymptomatic cases (54%) had abnormal CT findings (144).

**Chest CT lacks however in specificity.** Indeed, the typical radiological findings of COVID-19 overlap with those of other viral pneumonias. The predictive values of Chest CT will therefore depend on the phase of the epidemic as well as the level of co-circulation of other viruses such as influenza.

### Serology

Immunological assays (via Elisa or immunochromatography techniques) have been developed for the measurement of circulating antibodies of COVID-19 patients.

**Total seroconversion rates** are high. According to Zhao et al, among 173 RT-PCR confirmed COVID-19 cases with acute respiratory infection syndromes and/or abnormalities in chest CT images, seroconversion rate was 93.1%, 82.7%, and 64.7% for total Ab, IgM and IgG respectively (145). In the
early phase of illness, within 7-days since onset, the antibody assays only presented a positive rate of 38.3%. In days 15 to 39 after onset, seroconversion rates increased to 100.0% for Ab, 94.3% for IgM and 79.8% for IgG. Similarly, in a study by Guo et al, analyzing 208 plasma samples from two cohorts from China, positive rates of 85.4%, 92.7% and 77.9% were reported for IgM, IgA and IgG respectively (146). Higher rates (+/- 95%) are being reported in several pre-print studies (147,148).

**Time to seroconversion**: The median seroconversion time for Ab, IgM and IgG was day-11, day-12 and day-14 after symptom onset in the study by Zhao et al (145,146). In Guo et al’s study, the median duration to IgM and IgA antibody detection were 5 days (IQR 3-6) and 14 days for IgG (IQR 10-18) (146). Both studies described higher sensitivities of the serological assays over a repeated RT-PCR after the first week of symptom onset.

Following these results, the authors have suggested that serology, in combination with RT-PCR, may have an added value in the diagnostic work-up of suspected COVID-19 cases in the second phase of the disease.

**Data on seroconversion in asymptomatic and pauci-symptomatic cases** is scarce but emerging. Investigation of a family cluster of 2 patients and 4 close contacts, showed IgM detection in all family members, including the 4 close contacts despite absence of significant clinical symptoms (146). In a serological survey of 164 close contacts, among the 16 that screened positive with RT-PCR, all were positive in IgG or/and IgM, including 3 that had no symptoms (148).

**Considering specificity**, Guo et al found strong cross reactivity of their serological assay with SARS-CoV. In contrast, no cross-reactivity was found with the other human coronaviruses (NL63, 229E, OC43, HKU1). In addition, no anti-SARS-CoV-2 IgM, IgA, or IgG antibodies were detected in 185 control samples (samples from healthy individuals and patients with acute lower respiratory tract infections) (146). Cross-reactivity has been found when sera from SARS-CoV-2 patients are tested using SARS-CoV serological assays (149). Whether false positives occur with other diseases (eg. autoimmune diseases) is not yet clear.

**Importantly**, due to insufficient hindsight, persistence of antibodies after COVID-19 is currently unknown. In SARS-CoV, its closest related human coronavirus, sero-persistence is reported for 1 to 2 years (130), possibly longer (131). Nevertheless, correlation between antibody levels and protection against re-infection or disease is currently unknown.

**Test validation**: A large number of in-house and commercial tests are being rapidly developed, of different qualities. Prior to implementation, tests must be registered and quality checked by the usual regulatory bodies.

### Rapid tests

Rapid tests have been developed with the idea of a point-of-care approach, offering rapid results (within 10-30 minutes). Two types of rapid tests have been developed:

**Rapid antigen tests**: These tests are immune-chromatographic assays, and involve the detection of SARS-CoV-2 antigen in samples such as naso-pharyngeal swabs. Initial test validation in Belgium has shown a high specificity (100%), but lower sensitivity (56-60%). These tests therefore have high positive predictive values, so that a positivity test can be interpreted as a true COVID-19 disease. In contrast, the lower negative predictive value of these tests (64-85% in this evaluation) means that all negative samples should be re-tested using RT-PCR (150).

**Rapid antibody tests**: These tests are immune-chromatographic assays developed for the detection of circulating SARS-CoV-2 antibodies. The tests provide rapid but only qualitative information (presence or not of IgM and/or IgG antibodies). The first peer-reviewed study in 397 patients with PCR-confirmed COVID-19 reported a sensitivity of 88% and a specificity of 90% (151). A recent comprehensive review indicated that the reported sensitivities of commercial kits vary from 45% to 100% (overall average of 91%). The specificity of the assays ranged between 90.3% and 100% (overall average 97%) (152). Positive results require a seroconversion, therefore these tests are not useful for early COVID-19 diagnosis or in the early stage of the disease (see section “serology”, in particular ‘timing to seroconversion’). As currently the correlation between antibody (levels) and protection against re-infection or disease is currently unknown, a positive test result can only inform of a past
infection. This will have to be taken into consideration when deciding on the clinical application of such tests, which has not yet been clearly defined.

Over 220 commercial rapid test kits have been developed from 20 countries, of variable performance (152). As with the other in vitro diagnostic medical devices developed for COVID-19 diagnosis, all rapid tests should be registered and quality checked by the usual regulatory bodies.

### Epidemiology

#### Overview

Source [ECDC](https://www.ecdc.europa.eu/en/novel-coronavirus-china): COVID-19 was first identified in Wuhan City (Hubei province, China) in December 2019: on the **31 December 2019** a cluster of 27 pneumonia cases of unknown aetiology, including 7 severe cases, was reported, with a common link to Wuhan’s Huanan Seafood Wholesale Market, a wholesale fish and live animal market. **By the 20 January 2020,** cases imported from China were confirmed in Thailand, Japan, and South Korea.

**The first imported European case** was reported from France on the **24 January 2020.** In Germany, cases were reported on **28 January 2020,** related to a person visiting from China.

On the **30 January 2020,** the WHO declared the outbreak a **public health emergency of international concern.**

In Belgium, the first confirmed case was reported on **03 February 2020,** an asymptomatic person repatriated from Wuhan.

**On 22 February,** the Italian authorities reported clusters of cases in Lombardy and cases in Piedmont and Veneto regions. **During the following 2 weeks,** several European countries, including Belgium, reported cases of COVID-19 in travelers from the affected areas in Italy, as well as cases without epidemiological links to Italy, China or other countries with ongoing transmission.

On the **11 March 2020** the Director-General of the World Health Organization declared COVID-19 a **global pandemic** and on the **13 March 2020,** that Europe was the new epicenter of the disease.

The epidemiological reports for Belgium can be found here: [https://epidemio.wiv-isp.be/ID/Pages/2019-nCoV_epidemiological_situation.aspx](https://epidemio.wiv-isp.be/ID/Pages/2019-nCoV_epidemiological_situation.aspx). A more detailed report is published weekly on Thursdays.

For international epidemiological updates:

- John Hopkins Coronavirus Resource Center: [https://coronavirus.jhu.edu/map.html](https://coronavirus.jhu.edu/map.html)

#### Effect of climate

**Impact of meteorological conditions** on the transmission dynamics of SARS-CoV-2 is currently under investigation. Seasonality is known for other beta-coronaviruses. OC43 and HKU1 cause annual wintertime outbreaks of respiratory illness in temperate regions suggesting that wintertime climate and host behaviors may facilitate transmission. Dissemination of MERS-CoV and SARS-CoV have also been associated with climate factors, possibly increased with lower temperatures and dry conditions (153–155). Concerning SARS-CoV-2, data is too preliminary to conclude. Studies evaluating effect of climate on outbreak dynamics across several countries have not taken into consideration country differences with regards to containment measures or disease-reporting system (156,157). Moreover, certain studies have considered meteorological parameters only, without correcting for other parameters impacting disease dynamics, such as population density, population age distribution, etc (158). However, in a Japanese study, the relationship between the accumulated number of patients per 1,000,000 population and the average temperature in each of the country’s prefectures was evaluated. Monthly number of inbound visitors from China and an old-age dependency ratio were added as additional explanatory variables in the model. A possible association between low temperature and increased risk of COVID-19 infection was found (159). Inversely, a spatio-temporal analysis exploring the effect of daily temperature on the accumulated number of COVID-19 cases in the different Spanish provinces found no evidence suggesting a reduction in case numbers at warmer
### Risk groups

**Older age:** has been repeatedly identified as the most important risk factor for severe COVID-19 disease. Out of a total of 44,672 confirmed cases in China (reported in China CDC Weekly), 87% of confirmed cases were aged between 30 and 79 years, and 3% were ≥80 years of age. Confirmed cases ≥80 years of age had the highest case fatality rate (CFR= 14.8%), followed by 70-79 year-olds (CFR=8.0%), and 60-69 year-olds (CFR= 3.6%) (106). In a retrospective cohort study by Zhou et al, including 191 hospitalized COVID-19 patients in Wuhan, multivariable regression showed increasing odds of in-hospital death associated with older age (odds ratio 1.10, 95% CI 1.03–1.17, per year increase; p=0.0043) (86). Liu et al have reported on another retrospective cohort study of hospitalized patients in Wuhan. Among 109 COVID-19 confirmed patients, 53 (48.6%) of them developed Acute Respiratory Distress Syndrome (ARDS). Compared with non-ARDS patients, in univariate analysis, patients with ARDS were older (mean age, 61 years vs. 49 years; p< 0.001), and more likely to have underlying comorbidities (161).

**Co-morbidities:** In a recent meta-analysis (10 articles, 76993 patients overall), the most prevalent underlying diseases found among hospitalized COVID-19 patients were hypertension, cardiovascular diseases, diabetes mellitus, smoking, chronic obstructive pulmonary disease (COPD), malignancy, and chronic kidney disease (162). In Liu et al’s study introduced above, ARDS-patients compared with non-ARDS patients were, in univariate analysis, more likely to have coexisting diabetes (20.8% vs. 1.8%; p=0.02), cerebrovascular disease (11.3% vs. 0%; p=0.01), and chronic kidney disease (15.1% vs. 3.6%; p=0.049) (of note, malignant disorders were excluded from this study) (161). In Zhou et al’s study, out of the 191 COVID-19 hospitalized patients included, 91 (48%) had a comorbidity, with hypertension being the most common (30% of patients), followed by diabetes (19%), and coronary heart disease (8%). All these co-morbidities, as well as chronic obstructive lung disease (3% of cases) and chronic kidney disease (1% of cases) were associated with non-survival in univariate analysis, but were not associated with increased odds of in-hospital mortality with multivariable regression (86).

**Gender:** In the above-mentioned report from China CDC weekly, males represented 51% of the confirmed cases (M:F ratio 1.06:1). CFR for men was 2.8% versus 1.7% for women (106). In the Lombardy (Italy) outbreak, a large retrospective case-series on 1591 COVID-19 patients admitted to ICU, 82% were male (114). In Zhou et al’s study, 62% of the 191 hospitalized patients were males. However, male gender was not identified as a risk factor for in-hospital death (86). Similarly, in Liu et al’s study of 109 admitted COVID-19 patients, 54% were males and no association with gender was found when comparing non-ARDS and ARDS patients (161).

**Smoking:** Various observational studies have included “smoking” among variables assessed for association with severe COVID-19 or progression to death. However, definitions used have varied, with some researchers using “current smoking” and others “history of smoking” as potential risk factor. In Zhou et al’s study described above, current smoker (versus non-smoker) was not significantly associated with in-hospital death (86). In another retrospective cohort study including 78 patients with COVID-19-induced pneumonia, an efficacy evaluation at 2 weeks after hospitalization indicated that 11 patients (14.1%) had deteriorated, and 67 patients (85.9%) had improved/stabilized. The progression group had a significantly higher proportion of patients with a history of smoking than the improvement/stabilization group (27.3% vs. 3.0%, χ² = 9.291, p = 0.018). Multivariate logistic analysis indicated that, like age, history of smoking (OR, 14.285; 95% CI: 1.577–25.000; P = 0.018) was among the risk factors for disease progression (163).

**Ethnicity:** Role of ethnicity has been insufficiently studied and reported in COVID-19 surveillance, and concerns with regards to morbidity and mortality in black and minority ethnic communities have been recently raised (164,165), warranting investigation. Ethnicity is a complex entity composed of genetic make-up, social constructs, cultural identity, and behavioural patterns, that all may influence COVID-19 disease.
### Health-care workers: cfr section on health-care workers in ECDC document 'Disease background of COVID-19'.

**Children**

Children seem to be less affected by COVID-19 than adults. Analysis of 72,314 confirmed cases in China showed only 0.6% of cases occurred in <10y and 0.7% of cases in children 10-19y (106). Very importantly, the same analysis reported zero deaths in children <10 years and one out of 549 children between 10 and 19 years. Similarly, low case numbers are reported in children in Europe: as of 13 May 2020, only 0.7% of the 576,024 laboratory-confirmed cases reported to the ECDC was <4 year old, 0.6% was 5-9 years and 0.9% was 10-14 years (166). Some have argued that children are less likely to get infected due to a difference in receptors (167) or immune imprinting by other viruses (168). Whilst some data seem to show that children are equally likely to get infected (67), several studies have shown lower attack rates in children (169–171). Additionally, the low reported numbers for children could partly be due to restrictive testing strategies limited to severe presentations, whilst it seems clear that children—even neonates—generally present no or mild symptoms (61,94,167,172–177). Most children were infected within their households (178) and rarely seem to be the index case of a cluster (179,180). The World Health Organization also noted in their Report of the WHO-China Joint Mission that “people interviewed by the Joint Mission Team could not recall episodes in which transmission occurred from a child to an adult” (42).

Mid-April, various sources including public health institutions alerted on an observed increase in the number of children presenting with a toxic shock-like syndrome with clinical features similar to Kawasaki disease, in both children with and without confirmed COVID-19 disease. Small case-series and case reports on such cases have also been published (181,182). Kawasaki disease is a multisystem vasculitis of unknown origin affecting young children. Previously, trigger of the disease by various infections has been suspected, including common coronaviruses (183,184). Kawasaki disease has epidemicity and seasonality, supporting the hypothesis that infection is involved (183). Although the disease is rare and that a large majority of children recover, awareness of its possibility and clinical presentation by first-line physicians and pediatricians is essential. Indeed early diagnosis and prompt treatment is critical to avoid complications, particularly those affecting the coronary arteries (g. aneurysms) (185).

### Pregnant women

Both SARS and MERS had high case-fatality rates in pregnant women who were therefore considered key at-risk populations for COVID-19 based on theoretical concerns (186). However, currently available data, albeit limited and based on small case series, reports similar clinical characteristics in pregnant women as in the general population (187–192). PCR testing on amniotic fluid, cord blood, and breast milk has been found to be negative in 15 cases (189,191). However, vertical transmission, be it very rare, might be possible. ACE2 receptors are highly expressed in maternal-fetal interface cells (193). A review of case reports identified 64 newborns born to COVID+ pregnant women, of which two infants tested positive 36h after cesarean delivery, indicating likely vertical transmission (192). A case series of 33 newborns in Wuhan, reported 3 infants with positive nasopharyngeal swabs on day two of life (194). Another 3 possible vertical transmissions have been reported based on presence of IgM in cord blood (195,196). In two out of three infants, PCR testing was also carried out and was negative. Importantly, all infants were clinically well and had normal birth weights. More evidence is needed to confirm the potential of in utero infection, as IgM-detection alone has known several technical constraints in the diagnosis of other congenital infections (197).

### Other special populations

**HIV patients:** Initial case reports and small uncontrolled case-series suggest that the clinical spectrum and disease course of COVID-19 in people living with HIV (PLHIV) is similar to that in HIV-negative persons(198–202). Even in severely immunocompromised PLHIV (although underrepresented in these publications), mild presentation and recovery from severe disease has been described (199,202). Similarly, the few available case-reports of SARS-CoV or MERS-CoV infection in patients with AIDS described mild disease symptoms and recovery (203,204). Thus, at present, there is no evidence to suggest that there is an increased risk of infection nor of developing severe COVID-19 in PLHIV who have achieved viral suppression through antiretroviral treatment and do not have a low CD4 count. Considering untreated PLHIV or those with advanced disease, data is still too scarce to...
conclude, although no alarming signals have been notified so far. Notably, the fatal cases of COVID-19 in PLHIV that have been reported frequently present additional risk factors, such as age and cardiovascular disease. As expressed in the EACS and BHIVA statement of the 30th April, “almost half of people living with HIV in Europe are older than 50 years and chronic medical problems, such as cardiovascular and chronic lung disease, are more common in people living with HIV”. PLHIV may therefore be at increased risk of complications because of additional COVID-19 risk factors. Finally, concerns have been raised with regards to the impact the COVID-19 outbreak on the HIV continuum of care, with risks of limited access to testing, care and treatment, related to lockdown measures (205,206).

**Solid cancer patients:** Initial studies from China reported a high prevalence of patients with solid cancer among COVID-19 cases, as well as greater risk of progression to severe disease in these patients (207–210). Higher proportions of patients with lung cancer (209–211) and colorectal cancer (208) were also reported. However, these studies had major limitations in terms of study set-up and analysis (212,213). With relatively small sample sizes and a high heterogeneity of cancer type and course of disease included, current evidence remains insufficient to conclude on an association between solid cancer and an increased risk for COVID-19 and/or a poorer prognosis. Confounders, such as additional risk factors including older age (208,209,211), higher rates of smoking history (212) and significant comorbidities may play a greater role that factors related to the cancer itself (214,215), but reminds us that these patients represent a vulnerable population. Importantly, a higher risk of clinically severe events for patients who underwent anti-tumor treatment, like chemotherapy or surgery in 2-4 weeks has been suggested (209,210), and warrants further investigation.

### Patient management

**Treatment**

Symptomatic and optimal supportive care is currently the mainstay of treatment for COVID-19 (e.g. antipyretics, oxygenation, ventilation, fluid management, treatment of co-infections or superinfection), and no COVID-19-specific treatment has been identified to date.

However, multiple treatment strategies, including re-purposing of older drugs, are under investigation. An interim guidance for the treatment of hospitalized cases in Belgium is available [here](#) and includes a review of literature and a summary of the ongoing clinical trials in Belgium.

Many questions have also arisen with regards to the use of Non-steroid anti-inflammatory drugs (NSAIDs), Angiotensin-converting enzyme inhibitors (ACEi)/Angiotensin receptor blockers (ARBs), and corticosteroids in patients. Self-medication & the interruption of chronic treatments without medical advice is strongly discouraged.

**NSAIDs:**

There is currently no scientific evidence establishing a link between NSAIDs and worsening of COVID-19. This was confirmed by EMA (European Medicines Agency) and FDA (Food and Drug administration) on the 18th and 19th of March respectively (216,217). Both agencies will continue to monitor events. Belgium’s treatment guidelines indicate that “As a precautionary measure, whilst awaiting pending results, paracetamol may be preferred as first-line symptomatic treatment of pain and fever (at usual dosage), while NSAIDs should be used with caution and according to common practice (contra-indicated in case of renal failure for example)” [link](#).

**ACEi/ARBs:**

A hypothesis has emerged on a potential increased risk of severe COVID-19 in patients taking ACEis and ARBs (218,219). This hypothesis is based on (i) ACE2 is the principal functional receptor used by SARS-CoV-2 for cell invasion, (ii) expression and activity of ACE2 receptor in various organs is increased after intravenous infusions of ACEi and ARBs in animal experiments, (iii) the identification of hypertension, diabetes, and cardiovascular disease as potential risk factors for severe SARS-CoV-2 (220), (iv) the knowledge that patients with these conditions are frequently treated with ACEi and ARBs (221). However, there is currently no data proving a causal relationship between ACE2 activity and SARS-CoV-2 associated mortality, and various counter-arguments to this hypothesis have been
A recent large cohort study has not found any impact of ACE/ARB use on mortality of patients hospitalized with COVID-19 in different countries (223).

On the 13th March, the Council on Hypertension of the European Society of Cardiology strongly recommended that "physicians and patients should continue treatment with their usual antihypertensive therapy because there is no clinical or scientific evidence to suggest that treatment with ACEi or ARBs should be discontinued because of the Covid-19 infection" (224). Belgian treatment guidelines currently state "there is currently no evidence from clinical or epidemiological studies that establishes a link between their use and worsening of COVID-19 [...]. It is important that patients do not interrupt their treatment with ACE inhibitors or ARBs nor be switched to other medicines, in spite of concerns raised in the social media related to the theoretical interferences between ACE2 receptors" link.

**Corticosteroids:** WHO guidance (13th March 2020) states the following: "Do not routinely give systemic corticosteroids for treatment of viral pneumonia outside of clinical trials", including COVID-19 for which "given the lack of effectiveness and possible harm, routine corticosteroids should be avoided unless they are indicated for another reason. Other reasons may include exacerbation of asthma or COPD, septic shock, and risk and benefit analysis needs to be conducted for individual patients" (225). However, there is currently no clinical or scientific evidence to support discontinuation of systemic or inhaled corticosteroid treatment indicated for a chronic pathology (inflammatory diseases, adrenal insufficiency, asthma* etc.). The clinical benefits of such treatments and the risks related to interruption being clearly established.

*The pneumology department of the University Hospital of Geneva has made a review on corticosteroids in suspected or confirmed COVID-19, with regards to pneumonia, acute asthma, acute exacerbation of COPD and ARDS (in French): link

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FACT SHEET
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15 MAY 2020, VERSION 4


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