Disclaimer:
This document has been written by scientists from the Epidemiology of Infectious Diseases Unit of Sciensano. Despite its recent discovery, over 45000 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and at the speed with which discoveries are being made, certain references included are preprint papers that have not yet been peer-reviewed.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 or updated since version 5 (14 June 2020):
Pathogen

**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 genome is split into 14 open reading frames, which include 16 nonstructural proteins and four structural proteins: the spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. The S protein is cleaved into two subunits, S1 and S2. S1 contains the receptor binding domain (RBD), and is involved in viral entry into host cells.

**Cell entry and viral replication:** Viral binding to the cells occurs via the interaction of the S protein of SARS-CoV-2, via the 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 replicate 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).

**Genetic diversity and SARS-CoV-2 variants:** Compared to other RNA viruses, coronaviruses have a genetic proofreading mechanism: a complex molecular machinery involved in maintaining the integrity of the SARS-CoV-2 RNA genome, preventing and repairing mutations. In consequence, the SARS-CoV-2 sequence diversity and overall evolutionary rate appear to be low. Nevertheless, viral mutations occur, and can rise in frequency either due to natural selection of favorable mutations, random genetic drift, or epidemiological factors. Currently, the main circulating variant of SARS-CoV-2 is the D614G variant (also referred to as G614), resulting from an A-to-G amino acid change caused by a single nucleotide mutation at position 23,403 in the Wuhan reference strain (D614). Initially originating in China, this variant emerged in Europe, and went on to become the globally dominant...
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strain over the course of a month: as SARS-CoV-2 is transmitted more rapidly than it evolves, the viral population is becoming more homogeneous.

Based on CT-value analysis, it has been suggested that the G614 variant is associated with potentially higher viral loads but not with disease severity (5). Nevertheless, higher viral loads do not prove *per se* an increased transmission potential, and the debate whether G614 is more infectious than D614 is ongoing, as nicely summarized by Grubaugh et al (6). Moreover, according to the authors, although the G614 mutation is located in the S protein, it appears unlikely that it would have a major impact on vaccines in the pipeline or drastically affect antibody-mediated immunity as the RBD of the virus is not affected by this locus. An additional study, performing phylogenetic, population genetics, and structural bioinformatics analyses of 18 S14 sequences, also concluded that a vaccine candidate based on the Wuhan reference strain is likely to be efficacious against all currently circulating lineages (7). However, it still remains unknown whether, in the long run, a gradual accumulation of mutations could result in an ‘antigenic drift’ of SARS-CoV-2 that could impact vaccine-effectiveness, as seen in analogy with influenza (5).

**Reservoir**

*Last update 01 April 2020*

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 (8–10).

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 (11). 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 (12). Various wild mammals, as well as cats and dogs, also have ACE2 configuration that is predicted to bind with SARS-CoV-2 S protein (13,14).

**Physical and chemical resistance of the virus**

*Last update 15 May 2020*

In the absence of any ventilation, according to a recent study (15), 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 (16).

Like other coronaviruses, SARS-CoV-2 is very stable at 4°C but sensitive to ultraviolet rays and heat (inactivated within 5’ at 70°C). Furthermore, these viruses can be effectively inactivated by lipid solvents and common disinfectants including ether (75%), ethanol, chlorine-containing disinfectant, peroxyacetic acid and chloroform (16,17).

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 (18) and the USA (19) and using dry heat (30’ at 65-70°C) in Germany (20). 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 (21).
### Prevention

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<td><strong>Last update</strong></td>
<td><strong>For the general public,</strong> 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 (22) and has been shown in a meta-analysis to be associated with a lower risk of viral transmission (23).</td>
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**Cloth masks**

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 (24). 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 (25–27). 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 (28–32). 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 (33). ECDC lists a number of potential risks and benefits without either recommending or discouraging the use (34). 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 (35,36) 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 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 (39).

<table>
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<th>Personal Protective Equipment</th>
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<td><strong>Last update</strong></td>
<td>WHO recommend the use of a <em>surgical mask, gown, gloves, and goggles or faceshield</em> for health care workers coming into close contact (&lt;1,5m) with possible or confirmed cases of COVID-19 (41). 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 (42).</td>
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**Surgical Masks vs. FFP2**

Different health care authorities have issued different advice on the recommended PPE (43), 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 (42), 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 (44,45). This conclusion was confirmed by a meta-analysis including six RCTs published very recently (13 March 2020) by the Chinese Cochrane Center (46). 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 (47).

WHO commissioned a large systematic review and meta-analysis on the effects of physical distancing, the use of face masks and eye protection on COVID-19 (23). The authors screened 20,013 records and included 172 studies in the systematic review and 44 comparative studies in the meta-analysis. The large majority of studies was done on SARS and MERS and all studies were observational. There was no direct comparison of protection offered by surgical masks with protection offered by respirators. All types of masks seemed effective in lowering the incidence of infections (unadjusted pooled RR 0.3 [0.20-0.44], low GRADE level of certainty). However, the effect seemed greater for N95 respirators than for surgical masks, albeit that there may be residual confounding due to greater use (and effectiveness of) respirators in health care settings and lacking information on aerosol-generating procedures. Moreover, important differences exist between the viral kinetics of MERS and SARS on the one hand and COVID-19 and Influenza on the other hand. Results of this recent review of observational studies on coronaviruses are in contrast with RCTs comparing surgical masks and respirators for protection against Influenza and other respiratory infections.

Therefore, N95/FFP2 masks should be used preferentially for aerosol-generating procedures, such as endotracheal intubation and cardiopulmonary resuscitation (48).

**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 (49). 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 (50). 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: (43,51)

- 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 (52). Some authors argue that certain other procedures/equipment may generate an aerosol from material other than patient secretions and 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 (48,49,51).

**Vaccine**

*Last update 4 September 2020*

There is currently no vaccine available against SARS-CoV-2 infection.

Considerable efforts are being deployed internationally to develop a vaccine. 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 (53).
An overview of vaccines in development can be found on the WHO website: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines.

A vaccine tracker, available at https://www.lshtm.ac.uk/research/centres/vaccine-centre/covid-19, lists COVID-19 vaccine candidates that are currently in Phase 1-3 trials, as well as major candidates in pre-clinical stages of development and research. On the 4th September, 234 vaccine candidates were identified and 39 are currently in clinical testing, of which 8 in phase III trials.

**Ventilation**

**Last update 18 September 2020**

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 (54).

**Increased ventilation has been shown to reduce airborne transmission** (55). In addition to increased ventilation, experts recommend limited room occupancy, avoidance of air recirculation (use ‘extraction mode when using air conditioning) and frequent breaks (56–60). If recirculation of air is necessary, HEPA filters or MERV13 can filter sufficiently small particles (57). Two-and-a-half air changes have been reported to eliminate 90% of airborne contaminants (61). Opening doors and windows can generate around 5-17 air changes per hour (ACH) (55,62).

In two pre-print articles (not peer-reviewed and with several limitations), the effect of ventilation on the risk of infection is calculated on the basis of mathematical models. For example, Dai and Zhao state that at least 3-10 ACH are required to obtain a risk of infection of <1% during a half-hour bus ride with an infected person (63). Buonanno and colleagues calculated that in a fitness centre with a ventilation of 0.5 ACH the risk of infection is 1% after 55 minutes, whilst increasing ventilation to 3 ACH can prolong the ‘safe’ time to 110 minutes (64). Dai and Zhao emphasize that the use of mouth masks by both the index person and his contact person can drastically reduce the risk of contamination and thus the number of ACH required.

**Clinical Aspects**

**Modes of transmission**

**Last update 18 September 2020**

Evidence indicates that SARS-CoV-2 is transmitted from human to human by infectious droplets (65). Contact tracing studies confirm that prolonged close contact is the main risk factor for transmission and that the risk of infection is much higher in household contacts compared to non-household contacts (66,67). Transmission may also occur indirectly through infected surfaces or fomites (68).

SARS-CoV-2 viral RNA has not only been found in upper respiratory tract secretions, but in many other body fluids such as faeces, blood and (very rarely) urine (69–71). Especially in faeces, viral RNA seems to be present later and persists longer than in samples from the upper respiratory tract (72). **Faeco-oral transmission** therefore needs to be considered. Importantly though, presence of viral RNA does not equal infectious potential. A German team analyzed samples from 9 patients but 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. **So far, three studies have managed to culture SARS-CoV-2 from stool samples** (69,73,74) but no cases of faeco-oral transmission have been documented (68). 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 (75). For this reason, ocular protection (goggles, faceshield) is part of the standard PPE for health care workers when in close contact with cases (cfr section PPE).

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

To this date, the scientific community continues to debate the potential of **airborne transmission** of SARS-CoV-2. Whilst it is undisputed that SARS-CoV-2 can survive in experimental aerosols (15,76) the implication in real-life circumstances is far less clear. An evidence summary identified 8 studies in which air samples were taken in hospitals to detect SARS-CoV-2 (77). In 6/8 studies viral RNA was found in the air. However, the detected amounts of RNA were very small and it is unclear whether it
Concerned viable virus as respiratory viruses are often inactivated by e.g. exposure to UV light or dehydration. In 3/6 studies, viral culture was attempted. In one it was not successful (78) and unclear in another (79). In the third study, a very recent pre-print (80), authors argue that issues with the sampling process hinder viral culture. With a different technique, they collected air samples in the room of a COVID-19 patient, during 3h and at a maximal distance of 4.8m. They were able to isolate viable virus. Other evidence pointing towards the possibility of airborne transmission comes from experiments with ferrets (81,82) and previous experience with SARS (83–85). Airborne transmission appears to best explain outbreaks such as in a South Korean call centre (94 people became infected on the 11th floor of an office building, with no clear relation to distance to the index case) (86), in fitness centres during Zumba classes (87), during a choir rehearsal (88), in a restaurant without fresh air supply but air being recirculated by the air conditioning (89) or among Chinese bus passengers (90). Reassuringly, all these outbreaks involve prolonged exposure in poorly ventilated areas.

For the potential of intrauterine mother-to-child transmission, see section ‘Pregnancy’.

### Incubation period

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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 (91–93). 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 (94).

Larger studies and meta-analysis have since been carried out, and confirm a median incubation period ranging between 5 and 6 days (95,96). In a study by Yang et al analyzing 178 cases and 131 transmission chains in Hubei province, 95% of symptomatic cases developed symptoms within 13.7 days (95% CI 12.5–14.9) of infection, and 99% within 17.8 days (95% CI 15.9–19.7) (95).

### Contagious period

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Beginning of contagious period: Viral load in the upper respiratory tract is highest around the day of symptom onset, followed by a gradual decline over time (97–104). A recent meta-analysis of 21 studies aiming at understanding antibody and viral RNA detection kinetics during SARS-CoV-2 infection, found that detection of RNA from upper respiratory tract samples was higher at symptom onset (105).

Throughout the epidemic, evidence of pre-symptomatic transmission has accumulated (100,106–110). A study by He et al used publicly available data from 77 transmission pairs to model infectiousness, using the reported serial interval (the period between symptom onset in infector-infected) and combining this with the median incubation period. They conclude that infectiousness peaks around symptom onset. The initial article stated that the infectious period started at 2.3 days before symptom onset. However, a Swiss team spotted an error in their code and the authors issued a correction, stating the infectious period can start from as early as 12.3 days before symptom onset (111). Nevertheless, the new calculations still indicate that <0.1% of the transmissions take place before 7 days prior to symptom onset, 1% of the transmissions before 5 days and 9% of the transmissions takes place before 3 days prior to the onset of symptoms (103).

Pre-symptomatic transmission is also illustrated by data from cluster investigations. In a detailed analysis of cases and contacts in Singapore, 7 clusters with likely pre-symptomatic transmission were identified (112). In South Korea, a large outbreak occurred among fitness instructors and attendees where the index patient developed symptoms only 3 days after the workshop (87).

There is still much uncertainty about the weight of pre-symptomatic transmission on the overall dynamics of the pandemic. A systematic review found that modelling studies predict that 40 to 60% of all SARS-CoV-2 infections are the result of transmission from pre-symptomatic individuals (113). The proportion assumed by He et al lies within this range (44%). In contrast, contact tracing studies report much lower proportions. In the study from Singapore, only 10/157 (6.4%) locally acquired cases were caused by pre-symptomatic transmission (112). Similarly, early data from Lombardy (Italy) showed only a limited number of asymptomatic cases identified through contact tracing, suggesting a minor role for asymptomatic individuals in the overall spread of infection (94).

As coughing and sneezing increase the amount of droplets that are expelled, the highest transmission potential (in absence of containment measures) would still reside in symptomatic individuals. In line
with this, several studies indicate that persons with symptoms are more likely to transmit the virus than those without. Four individual studies from Brunei, Guangzhou China, Taiwan, and the Republic of Korea have shown that between 0% and 2.2% of people without symptoms at the moment of contact have infected someone else, compared with 0.8% to 15.4% of people with symptoms (86,106,114,115). In the study in Brunei, household attack rates of symptomatic cases were higher (14.4% [95%CI: 8.8,19.9]) than pre-symptomatic cases (6.1% [95%CI: 0.3,11.8]). A study in China looked at the ratio of pre-symptomatic versus post-symptomatic transmission and examined 468 COVID-19 cases. They reported that 12.6% of transmission occurred prior to the onset of symptoms (108).

Currently, as in Belgium, contact tracing guidelines from Europe (France, Germany, The Netherlands, UK), ECDC (9 April), WHO (10 May) and the CDC (10 September) consider all potential contacts of a case from 48h before symptom onset.

**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 104 days (116), and several studies report positive tests up to 82 days after initial negative results (117,118). Viral shedding does however not equate with contagiousness, and no infectious virus has been isolated after D8 after symptom onset (97,119), see also topic ‘transmission’. Moreover, a “positive” RT-PCR result does not in itself reflect viral load, that can be estimated using RT-PCR cycle threshold (Ct) values. Ct levels are inversely proportional to the amount of target nucleic acid in a sample. Among RT-PCR positive respiratory samples, those with Ct values > 24 (i.e. with lower viral loads) have been shown to have reduced infectivity in vitro (119).

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) (106).

## Asymptomatic infections

Asymptomatic infection at the time of laboratory confirmation has been reported from many settings (94,120–125). A large proportion (57–89%) of these cases developed some symptoms at a later stage of infection (126–128), although there are reports of cases remaining asymptomatic throughout the whole duration of laboratory and clinical monitoring (122–125). 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 (CI): 15.5-20.2%) (121); according to data from Shenzhen (China), 20% of PCR-positive close contacts were asymptomatic at the time of testing (66); 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%) (122). In Iceland, citizens were invited for testing regardless of symptoms. Of all people with positive test results, 43% were asymptomatic (129). 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.(130) 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 (131). 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 (132) Similar viral loads in symptomatic vs. asymptomatic cases have also been reported in several other studies (94,98).

## 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 (93). Other symptoms include fatigue (23%), myalgia (15%), and gastrointestinal symptoms (+-8%) (133). 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. erythematous rash, widespread urticaria) (134–137). 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 (138,139). Notably, anosmia has been reported after infection with other respiratory or coronaviruses (140).

Data from more than 72,000 cases from China classified cases as mild (81%), severe (14%), or critical (5%) (141). 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).

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-ischaemia, disseminated intravascular complications, bacterial or fungal superinfections etc.) (142,143).

COVID-19 may also present with silent hypoxia. This phenomenon refers to a state of severe hypoxia associated with little or no respiratory symptoms such as dyspnea. It results from concomitant hypoxia and hypocapnia, a state that does not lead to the stimulus of the respiratory center of the brain. These patients go from a seemingly stable clinical state to a rapid deterioration of respiratory function within a few hours. Silent hypoxia is not unique to COVID-19, and a similar phenomenon is found with other diseases (high altitude hypoxia, heart shunt due to congenital heart disease, intra-pulmonary shunt due to lung disease etc). The exact physiopathology behind the development of hypoxia with hypocapnia in COVID-19 disease remains to be established. Although silent hypoxia is cited as a “common” clinical form, particularly in the elderly (144), only few case reports are found in the scientific literature (145,146) and testimonials from front-line physicians in the media (link). The frequency and risk factors of silent hypoxia in COVID-19 cases remain currently undefined.

Evidence is emerging that COVID-19 is associated with an increased risk of thromboembolic disease (147,148) and a high rate of cardiovascular complications (137). 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) (149). In a double-center study in the Netherlands, a 31% incidence of thrombotic complications in ICU patients with COVID-19 infections is reported (150).

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, co-morbidities). In early stages of the outbreak, CFR was 17% in China but decreased to 0.7% (47). In Wuhan, in admitted patients, mortality reached 25% in the middle of the epidemic (133). On March 22, the CFR in the oldest age group (>80y) in Italy was 23% (151). 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% (152). For Belgium, mortality is reported within the daily and weekly epidemiological reports (link).

In children, reports of a Kawasaki-like disease are increasingly reported, see section epidemiology > children.
Immunopathogenesis

Pathogenesis
Last update 15 May 2020

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 (153). 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 (153).

Persistence of high viral loads has been associated with disease severity (154). 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 (155). 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 (156). 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 TNFa were significantly higher in intensive care unit (ICU) patients than non-ICU patients (157). 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 (158). 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) (156).

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 (159).

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 (133,142,160,161). 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 (133). 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 (161). 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 (162).

An additional mechanism of disease pathogenesis hypothesized by several authors is antibody-dependent enhancement (ADE) (163,164). 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 (165). Whether ADE is involved or not in SARS-CoV-2 disease pathogenesis is still unknown.

### Immunity

**Humoral response:** The majority of COVID-confirmed patients develop SARS-CoV-2 specific antibodies (IgM, IgA and IgG) against the viral S and N protein within 1-3 weeks after symptom onset, that remain elevated after initial viral clearance. The kinetics of SARS-CoV-2 specific antibodies are developed in section on 'Serology' below.

Notably, the level of the antibody response mounted after infection shows a positive correlation with the degree of disease severity (166–169). In addition, longitudinal follow-up of COVID-19 patients have shown that antibody levels may rapidly wane, declining within 2 months after symptom onset, in particular after asymptomatic or mild infection (167,168). Conversely, in a nationwide study from Iceland, over 90% of PCR-positive persons tested positive with pan-ig assays and remained seropositive 120 days after diagnosis, with no significant decrease of antibody levels (169). Type of assay used and methodological design may explain the dissimilarities between studies. Similarly, according to Seow et al, if in a majority of individuals IgM and IgA rapidly declined, IgG levels remained high during the 94 day study period, although differences were seen with regards to their neutralizing potential (see nAbs below) (166).

Although antibodies are usually a reasonable correlate of antiviral immunity, it is important to note that data so far does not allow to affirm that the detection of SARS-CoV-2 antibodies indicates immunity to subsequent infection (carriage or disease), and their use as a correlate for disease protection needs to be further explored. Also, their absence after infection may not exclude acquired immunity as other immunological response mechanisms may be at play, in particular the T-cell response.

**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 SARS-CoV-2, the S protein epitopes, including RBD epitopes, are the main targets of nAbs (170,171). In a rhesus-macaque COVID-19 model, titers of nAbs linearly increased after primary infection and may have contributed to the subsequent protection from reinfection observed upon a second viral challenge on day 28 (172). However, in humans, a clear relationship between the presence of nAbs and protection against reinfection by SARS-CoV-2 has not yet been established.

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 (173). In this study and others, the magnitude of the nAb response, as for total antibody levels, correlated with disease severity (166,173). In the above mentioned longitudinal study by Seow et al, assessing the kinetics of nAbs in 65 PCR-confirmed COVID-19 cases, nAb titers peaked on average at day 23 post-onset of symptoms, and then decreased 2- to 23-fold during the 18-65 days follow up. In individuals that had developed only modest nAb titers following infection, nAbs became undetectable or approached baseline after +/- 50 days. In contrast, those with high peaks of nAb titers maintained these level for >60days (166).

Of interest is the experience we have acquired from related viral infections. With the closely related SARS-CoV-1, antibodies (including nAbs) have been shown to persist for 1 to 2 years, possibly longer.
(174,175). 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 (176). However, protection against reinfection, 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 (177).

**Cellular response:** 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 (178). Authors concluded that, despite antibody levels waning and low Nabs titers in convalescent patients, the T-cell response detected may play a key role in preventing reinfection and severe disease.

The potential role of specific T-lymphocyte immunity in protection from reinfection by SARS-CoV-2 also warrants investigation. Studies have shown that, after exposure, virus-specific T cell responses can be developed even in the absence of seroconversion (preprint) (179), and robust memory T cell responses have been detected after asymptomatic and mild-infections (180). This topic will be covered in greater depth in a future update.

**Population immunity:** The results of population-based sero-epidemiological studies in the general population and in blood donors of the EU/EEA Member States are available at https://www.ecdc.europa.eu/en/covid-19/latest-evidence/immune-responses: “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 in 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”.

**Reinfection**

The possibility of early reinfection (or viral re-activation?) was raised following several press-releases on suspected cases of reinfection 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 have been described (117,118), however, false negative RT-PCR result or prolonged viral clearance rather than recurrence of infection were suspected (118).

The Korean CDC published a report on the epidemiological and contact-investigation of 285 re-positive cases. Re-positive cases were detected either through screening (59.6%) or because of symptoms (44.7%). Time from initial symptom onset and re-positivity sampling ranged from 8 to 82 days (average 44.9days). Additional virological testing was performed for 108 of these re-positive cases: low viral loads were found in a majority of cases (89.5% had Ct values >30) and viral cell culture was negative for all. For these re-positive cases, 790 contacts were identified, among which only 3 newly-confirmed cases were identified. These 3 cases had additional high-risk exposures to COVID-19 to the exposure to the re-positive case. Overall, no evidence indicating infectivity of re-positive cases was found (181).

In August 2020, the first published case of a SARS-CoV-2 reinfection was reported in Hong Kong. Epidemiological, clinical, serological and genomic analyses (SARS-coronavirus-2 strains phylogenetically distinct) confirmed that the patient had a reinfection and not a persistent viral shedding from the first infection (182). The first infection was a mild symptomatic episode, the second was an asymptomatic infection detected through screening upon return from travel. Three additional cases of reinfection have been reported based on a high degree of genetic discordance upon genomic analysis of the viruses. The first concerns a 25 year old man, with a first mild episode and a more severe second episode (hospitalization and O2 requirement) two months later (183). The second is a 46 year-old man from Ecuador, with a slightly more severe infection (albeit not requiring hospitalization) a month later. The third, a 51 year-old woman living in Belgium, was diagnosed with a milder infection 3 months after a first episode (184). An additional case of reinfection, occurring in the Netherlands in an immunocompromised elderly, was declared in a news report. These cases may be exceptions and a reinfection is still considered as a rare event. However, the overall incidence and therefore risk of reinfection is currently unknown, particularly as full-length genome sequencing is required to
distinguish re-positivity from reinfection (185). Greater hindsight on the frequency of such events will be acquired with a second wave of infections.

**Diagnosis**

**Overview**

Last update 19 April 2020

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**

Last update 01 April 2020

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 (133).

**RT-PCR**

Last update 16 September 2020

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.

- **Timing and type of specimen**: the overall quality of studies assessing 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, primers and probes used for assay not described etc. Nevertheless, important information is emerging.

  With regards to timing of testing and impact on sensitivity: In a literature review and pooled analysis, Kucirka et al analyzed the rate of false negative RT-PCR on upper respiratory tract samples of COVID-19 symptomatic patients (in- & out-patients) in relation to the number of days since exposure (186). Day 5 was used as an estimate for the onset of symptoms. The probability of a false-negative result decreased from 100% (95% CI, 100% to 100%) on day 1 to 67% (CI, 27% to 94%) on day 4. On the day with onset of symptoms the probability of a false-negative rate was 38% (CI, 18% to 65%). This decreased to 20% (CI, 12% to 30%) on day 8 (3 days after symptom onset) then began to increase again, from 21% (CI, 13% to 31%) on day 9 to 66% (CI, 54% to 77%) on day 21. Considering these trends is essential, however heterogeneity in the design of the studies included in the pooled analysis may have led to imprecision of the estimates. Results are not to be extrapolated to asymptomatic cases.

  With regards to sample type: Sensitivity of RT-PCR appears to be higher for lower respiratory samples than for upper respiratory tract samples (69,97,187). 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.
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 (98–101). RT-PCR may remain positive longer in lower respiratory samples (97,187). In a prospective cohort of 67 COVID-19 pneumonia cases (Chonqing, 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 (187).

Testing saliva samples (spit in a container or swab) instead of using nasopharyngeal swabs (NPS) for RT-PCR has been suggested. It could overcome a possible shortage of swabbing material, facilitate the sampling procedure, decrease discomfort of sampling, decrease exposure risks and, through self-sampling, decrease the workload of health care workers. Small studies and 2 meta-analysis have shown a high concordance and no significant difference in sensitivity between RT-PCR on saliva samples and NPS (188–192). In contrast, lower sensitivities on saliva compared to NPS have also been reported (193,194) and some have even suggested a sensitivity below 70% for saliva (195,196). A Belgian study (not yet peer reviewed) with 2000 persons demonstrated a correspondence of 97% between NPS and saliva samples with medium and high viral loads (above 20.000 copies/ml), but <5% correspondence with low viral loads (below 20.000 copies/ml) (197). In the same study, it was suggested that the detection sensitivity was much better for saliva collection in a container compared to a saliva swab. Studies on SARS-CoV-2 saliva testing in asymptomatic persons are limited. In a recent study, 13 of 495 asymptomatic healthcare workers tested SARS-CoV-2 positive on saliva. From the 9 self-collected matched NPS specimens, 7 tested negative. An additional NPS sample of the 13 health care workers was tested later by a CLIA-certified laboratory and all were positive (198). Rao et al. demonstrated in asymptomatic persons in quarantine, a higher detection rate for SARS-CoV-2 in early morning saliva compared to NPS testing (93.1%, 149/160 vs 52.5%, 84/160, p<0.001) (199). One study has evaluated the suitability and sufficiency of self-collected samples. For saliva samples, clinical observers assessed that 96% of the samples were of sufficient quality for laboratory testing and quantitative laboratory assessment gave a Ct value (for RNase P) below 30 in 99% of the samples (200). Overall, the current studies evaluating saliva testing often have a limited sample size and differ regarding type of saliva (deep throat, drooling,...), collection method/device (container/swab; self-collected), timing of sampling (early morning), study population (asymptomatic/symptomatic/hospitalized) making it difficult to draw conclusions. More and bigger studies are needed to determine the most suitable population for saliva testing, the best type of collection method and optimal sampling time for diagnosis and screening.

• **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 (201,202), and assays have used different primers and probes. Instructions for test validation in Belgium are available in Fr and Nl.

Specificity of RT-PCR for the diagnosis of COVID-19 is high (in the order of >99.5%) (203). With the exception of SARS-CoV, no cross-reactivity is found when tested against a large panel of microorganisms including the common human coronaviruses (204). 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

**Last update 19 April 2020**

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 (205).


**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 (206). Inversely, negative Chest CT in PCR positive patients has also been reported (207), 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 (208). 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 (209). 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 (125). Similarly, on the “Diamond Princess cruise ship”, 41 out of 76 asymptomatic cases (54%) had abnormal CT findings (210).

**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

**Last update 18 September 2020**

Immunological assays, or serology tests, have been developed for the measurement of antibodies directed against SARS-CoV-2 proteins. Currently available assays target the main immunogenic coronavirus proteins: the N-protein, the S-protein or the Receptor Binding Domain of the S-protein (RBD).

**Kinetics of seroconversion:** Multiple studies have been published on time to and rates of seroconversion, as well as on the duration of the antibody response. Conclusions of a systematic review, published by the Health Information and Quality Authority of Ireland (update on August 6, 2020) (211) indicated that:

- Seroconversion rates are high, with SARS-CoV-2-specific IgG antibodies detected in over 90% of individuals at two weeks and 100% at four weeks.
- Immunoglobulin M (IgM) is typically the first antibody to rise in acute infection, followed by immunoglobulin G (IgG) with IgG tending to persist much longer in the body.
- The median time to antibody detection following symptom onset ranges from 5 to 17 days for IgM and 6 to 14 days for IgG.
- The persistence of antibodies after COVID-19 is still unclear. As mentioned above (cfr section “Immunity”), several studies showed that anti-SARS-CoV-2 antibodies wane overtime while others found antibody persistence for at least 120 days.
Correlation between antibody levels and protection against reinfection or disease is currently unknown (169,212).

Data on seroconversion in asymptomatic and pauci-symptomatic cases is emerging. Recent studies comparing the antibody response in hospitalized COVID-19 patients and in mild or asymptomatic cases, showed lower SARS-CoV-2-specific antibody responses in the mild or asymptomatic patients (213).

Serology assays: A diverse range of serological assays exist, of which ELISA (Enzyme Linked ImmunoSorbent Assay) is the most commonly used. Currently developed ELISAs for SARS-CoV-2 are semi-quantitative and can specifically detect antibodies (IgG, IgM, IgA or all Ig) directed against one specific protein (S, N or RBD).

Multiplex serological tests are also available. These tests simultaneously measure antibodies directed against several antigens (S1, S2, RBD, N, M, E,...)

Rapid antibody test also exist (description below).

Functional assays have been developed to measure the neutralizing capacity of anti-SARS-CoV-2 antibodies. These assays require the use of the wild-type virus or a pseudotyped virus, and are mainly used for research purposes.

All these tests can be used on one or several different matrices such as blood, serum, plasma, capillary blood, saliva,... Each test has to be validated for the intended matrix.

Performance of ELISA tests, cross reactivity: Many different serological tests have been developed for COVID-19, with variable sensitivities and specificities. Assay performance also vary depending on the purpose of the test (population screening or diagnostic in hospitals for instance) (214). A meta-analysis published in July reviewed 40 articles (January to April) and showed a pooled sensitivity of ELISA measuring IgG or IgM of 84.3%. Pooled specificities ranged from 96.6 % to 99.7 %. Sensitivity was higher at least three weeks after symptom onset (ranging from 69.9 % to 98.9 %)(215). A recent evaluation of COVID 19 serological assays found sensitivities ranging from 81 to 99 % and specificities ranging from 94 to 99 % (214).

Cross-reactivity between seasonal human coronaviruses and the pandemic SARS-CoV-2 needs to be carefully considered in the development and interpretation of assays for precise detection of SARS-CoV-2- specific antibodies. 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) (216). Inversely, cross-reactivity has been found when sera from SARS-CoV-2 patients are tested using SARS-CoV serological assays (217). Whether false positives occur with other diseases (eg. autoimmune diseases) is not yet clear.

Use of serology tests: The use of serology tests for diagnostic purposes is by consensus limited since RT-PCR remains the preferred diagnostic test. However serology tests can be used for specific diagnostic purposes such as for hospitalized patients with a suggestive clinical picture but divergence between RT-PCR and CT scan. Indications for which a serology test is reimbursed in Belgium can be found here.

IDSA recently (218).published recommendations in which potential indications for serologic testing are including: 1) evaluation of patients with a high clinical suspicion for COVID-19 when molecular diagnostic testing is negative and at least two weeks have passed since symptom onset; 2) assessment of multisystem inflammatory syndrome in children; and 3) for conducting serosurveillance studies.

Serological surveillance is also of crucial public health importance to monitor SARS-CoV-2 infection prevalence, i.e. the proportion of individuals in the population that have been in contact with the SARS-CoV-2 virus. Preliminary results of first sero-epidemiological population studies in EU Member States and the UK is available at https://www.ecdc.europa.eu/en/covid-19/latest-evidence/immune-responses
**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 (219).

**Rapid tests**

**Last update** 22 April 2020

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 (220).

**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% (221). 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%) (222). 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 reinfection 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 (222). 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**

**Last update** 01 April 2020

Source **ECDC**: 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).

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| Basic reproductive number | The basic reproductive number, the so-called R0, of the virus is thought to be between 2-4 (223) 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 (Rt) 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. Various modelling studies have reported on the level of reduction of the reproductive number following the implementation of non-pharmaceutical interventions such as closure of schools and national lockdown (which vary from country to country). In France, lockdown measures were estimated to reduce the reproductive number from 2.90 to 0.67 (77% reduction) (224). In the United Kingdom, "lockdown" patterns of social contact were compared to those during a non-epidemic period in a survey-based study. A 74% reduction in the average daily number of contacts observed per participant was reported. According to the authors, this would be sufficient to reduce the reproductive number from 2.6 to 0.62 (95% CI 0.37-0.89) after the lockdown (225). Similarly, a modelling study evaluating the impact of non-pharmaceutical interventions across 11 European countries up until the 4th of May 2020, concluded that measures have been sufficient to drive the reproduction number below 1, with an average of 0.66 across the included countries and 0.82 (95% CI 0.73 – 0.93) for Belgium (226). |

| 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 (227–229). 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 (230,231). Moreover, certain studies have considered meteorological parameters only, without correcting for other parameters impacting disease dynamics, such as population density, population age distribution, etc (232). 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 (233). 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 temperatures. Non-meteorological factors such as population density, population by age, number of travelers were considered in the analysis (234). |

| Special populations | 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%) (141). 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) (133). 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 elder (mean age, 61 years vs. 49 years; p< 0.001), and more likely to have underlying co-morbidities (235).

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 (236).

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) (235). In Zhou et al’s study, out of the 191 COVID-19 hospitalized patients included, 91 (48%) had a co-morbidity, 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 (133).

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 (141). In the Lombardy (Italy) outbreak, a large retrospective case-series on 1591 COVID-19 patients admitted to ICU, 82% were male (152). 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 (133). 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 (235).

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 (133). 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 (237).

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 (238,239), 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.


Genetics: Genetic determinants of severe COVID-19 are under investigation. A genome-wide association study (pre-print) comparing 1,610 COVID-19 patients with respiratory failure with the general population in Italy and Spain, reports two genetic susceptibility loci, one situated on chromosome 3 (3p21.31) and one on chromosome 9 (9q34.2) (240). The gene locus on chromosome 3 covers a cluster of several genes with potentially relevant functions in severe COVID-19, including a gene encoding SIT1 which functionally interacts with ACE2, and genes encoding chemokine receptors (CCR9 and CXCR6). For the gene locus on chromosome 9, the association signal was restricted to the ABO blood group gene. A blood-group-specific analysis showed a higher risk of COVID-19 respiratory failure for A-positive individuals (OR=1.45, 95% CI, 1.20 to 1.75) and a
protective effect for blood group O (OR=0.65, 95% CI, 0.53), in line with previous reports (241,242). Notably, no association with polymorphisms at the HLA complex were found. Other genetic determinants, such as polymorphisms of Angiotensin-Converting Enzyme 1 (ACE1) (D/I polymorphism, associated with alterations in circulating and tissue concentrations of ACE), have been suggested as a potential factor partly explaining the geographic differences of COVID-19 prevalence (243). However, the contribution of genetic determinants to the geographical differences in the COVID-19 epidemic remain unknown, such differences being largely influenced by multiple determinants (testing strategy, reporting, non-pharmaceutical interventions, population demographics etc.)remains unknown, being largely influenced by multiple determinants (testing strategy, reporting, non-pharmaceutical interventions, population demographics etc.)

- **Children**
- **Last update**: 10 September 2020

Children seem to be less affected by COVID-19 than adults and are more likely to have mild or asymptomatic infection. 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 (244). 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 (245). In Belgium, confirmed cases in children <18y until 28/06 made up 3% of total confirmed cases. Children were less likely to test positive (1.8%) compared to adults (6.3%) (report Sciensano). Both a meta-analysis and mathematical modeling concluded that children are about half as likely to get infected than adults (246,247). Some have argued that this is due to a difference in distribution, maturation, and functioning of viral receptors (248) or immune imprinting by other viruses (249). Research has shown that the expression of the functional receptor for SARS-CoV-2, ACE-2, within the nasal epithelium is lower in the lower age groups (250). It is also likely that pediatric disease is underdiagnosed as COVID-19 infections in children are usually asymptomatic or mild. Fever and cough are the most frequent symptoms. Reported proportions of severity vary internationally and within Europe (251–256). Young children seem either more (251,253) or less at risk (252,254,255) for severe disease. In Belgium, most of the hospitalized children (81%) had no severe event. Only a proportion of 3% was admitted to ICU (report Sciensano). Fatal outcome in children is very rare (CFR of 0.69%).

The role of children in the transmission dynamics of SARS-CoV-2 is under discussion (257) but it seems that children are not the drivers of transmission (258). Transmission of SARS-CoV-2 from children, even neonates, is plausible as shown by successful viral culture of the virus from PCR-positive samples of symptomatic children (259). In a large study including samples from 3,712 COVID-19 patients, viral loads (estimated by real-time RT-PCR threshold cycle values) in the very young were positive samples of symptomatic children (259). In a large study including samples from 3,712 COVID-19 patients, viral loads (estimated by real-time RT-PCR threshold cycle values) in the very young were significantly different from those of adults (260). However, transmission dynamics is not only determined by the biological component, also behavioral and contextual components are involved. Most children appear to be infected within their households (261). Based on contact tracing studies on household transmission, children rarely seem to be the index case of a cluster (in 8 to 10% of households) (262,263) while this is much higher for H5N1 influenza (54%) (262) and children rarely cause secondary cases (264,265). Data on transmission in school settings is limited but increasing. Contact tracing and cluster investigations in schools before lockdown done in Ireland (266), France (267,268) and New South Wales (269) report very limited onwards transmission. Finland and Sweden have very similar schooling systems but Sweden decided to keep primary schools open (pupils <15y). A comparison between both countries did not show any measurable impact of the school closure on the number of laboratory-confirmed cases in children (270). Data from Public Health England showed outbreaks were rare and mostly linked to staff. The risk of having an outbreak in a school correlated with the level of community transmission (271). Seroprevalence studies have demonstrated that the infection attack rate in high school students (38.3%) was higher than in primary school students (8.8%) (267,268). Caution is therefore needed, as also exemplified by a large outbreak in a high school in Israel, with an infection in 153 students and 25 staff members (272).

A syndrome related to SARS-CoV-2 is identified in children. 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, now referred to as...
Pregnant women

Disease severity: 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 (280). However, preliminary data from small case series, reported similar clinical characteristics in pregnant women as in the general population (281–286). More recently, these findings have been confirmed in obstetric surveillance data from the UK (287) and a prospective cohort from NYC (288). However, nation-wide data from Sweden and the USA indicated that pregnant and postpartum women are at increased risk for complications and ICU admission. In Sweden, out of 53 women that were admitted to ICU with SARS-CoV-2, 13 were pregnant (of which 7 required invasive mechanical ventilation). The risk of requiring ICU admission was significantly higher for pregnant women compared to non-pregnant women of the same age (289). Likewise, the US CDC analyzed data on 8,207 pregnant women and found pregnancy to be related with a relative risk of 1.5 [1.2-1.8] for ICU admission, after adjusting for age, presence of underlying medical conditions (yes/no) and race/ethnicity (290). Importantly, there was no increased mortality. Whilst these findings warrant further caution regarding COVID-19 in pregnancy, both studies come with important limitations. The Swedish report included only small numbers of women requiring ICU. In the CDC registry, data was missing on many variables, and info on pregnancy was only available for 28% of women in reproductive age. Both registries did not have data on the reason for ICU admission, which might be related to pregnancy but not necessarily to SARS-CoV-2. Moreover, based on changes in physiology, women would be deemed most at risk in the 3rd trimester of pregnancy but none of the registers accounted for gestational age, and pregnant women in ICU were as early as 13th weeks post-menstrual age. Finally, even though the relative risk might be increased, overall absolute risks in this age groups seem low.

Risk to the fetus: In utero transmission is possible, as proven by a case from France (291). After a cesarean delivery for fetal distress at 35w5d in a symptomatic SARS-CoV-2+ mother, a neonate was born with positive RT-PCR on cord blood, BAL and naso-pharyngeal swab. Placental histology and amniotic liquid also showed presence of SARS-CoV-2. The neonate was initially admitted to NICU and intubated but discharged at day 18 of life with a normal follow-up visit at 2 month of life. Whilst possible, vertical transmission seems however extremely rare (291–294). A systematic analysis of published reports identified a total of 655 women and 666 infants for which data was available. They found a total of 28 neonates, almost all asymptomatic, for which vertical transmission might have been possible, although they hypothesize that some false-positive nasopharyngeal swabs might be reported due to contamination by maternal stool (292). The fetus is thought to be relatively protected from SARS-CoV-2 because viraemia is rare and the required receptor and co-receptor for SARS-CoV-2 are seldom expressed simultaneously in the placenta (295). Pre-term and cesarean delivery rates seem related to geographical differences rather than being a result of COVID-19 (296). Some authors have warned for the possibility of intrauterine growth restriction (282), a concern that...
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| Other special populations | HIV patients: The few available case-reports of SARS-CoV or MERS-CoV infection in patients with AIDS described mild disease symptoms and recovery (299,300). Similarly, for SARS-CoV-2, initial case reports and small uncontrolled case-series have suggested that the clinical spectrum and disease course of COVID-19 in people living with HIV (PLWH) is similar to that in HIV-negative persons (301–306). Similar conclusions are drawn from more recent matched case-control studies comparing HIV and non-HIV patients, albeit limited in size (307,308). These results and publications are mainly from Europe, USA and China. The largest study on PLWH in Europe to date is from a Spanish cohort of 77590 HIV positive persons under antiretroviral therapy (ART), among which 236 were diagnosed with PCR-confirmed COVID-19 between February and mid-April 2020. After standardization to the age and sex distribution of Spain, the risk in HIV-positive persons for COVID-19 diagnosis was 30/10 000 and 3.7/10 000 for COVID-19 death. In comparison, risk of COVID-19 diagnosis and death in the Spanish general population aged 20 to 79 years during the same period was 42/10 000 (33/10 000 when excluding healthcare workers) and 2.1/10 000, respectively. The risks of COVID-19 diagnosis, hospitalization, ICU admission, and death in the ART-receiving PLWH were greater in men and those older than 70 years, consistent with the age and sex-patterns reported for HIV-negative persons. Also, the risk for hospitalization was lower in patients receiving TDF/FTC (tenofovir disoproxil fumarate /emtricitabine) based ART versus those receiving other regimens, a result warranting further investigation due to possible confounders, particularly co-morbidities, not captured in the study (309). In a population cohort study from the Western Cape Province of South Africa, in adjusted analysis, HIV increased the risk of COVID-19 mortality by a factor of 2.14 (95% CI [1.70; 2.70]), with similar risks across strata of viral load and immunosuppression. Current and previous tuberculosis also increased COVID-19 mortality risk (adjusted hazard ratio: 2.70 [1.81; 4.04] and 1.51 [1.18; 1.93] respectively). Authors concluded that, although the HIV-associated risk of COVID-19 death may be over-estimated due to residual confounding (co-morbidities, socio-economic status), people with HIV should be considered as a high-risk group for COVID-19 management. Of note, if the larger prevalence of HIV in Africa permits such studies with higher participant numbers, results may not be transposable to Europe, due to multiple differences in population characteristics (310). Overall, as expressed in the recent joint statement of the BHIVA, DAIG, EACS, GESIDA & Polish Scientific AIDS Society "Whether or not PLWH on treatment with a normal CD4 count and suppressed VL (viral load) are at an increased risk of serious illness or death, many will have other conditions that increase their risk. Indeed, almost half PLWH in Europe are older than 50 years and chronic medical conditions, including cardiovascular and chronic lung disease, are more common in PLWH". This is supported by a study of the multi-center research network TriNETX (USA), comparing 404 PLWH and 49763 non-HIV with COVID-19 diagnosis (patients>10y). If crude COVID-19 mortality was higher in PLWH, propensity matched analyses revealed no difference in outcomes, indicating that the higher mortality was driven by the higher burden of co-morbidities (311). Importantly, although mild presentation and recovery from COVID-19 severe disease has been described in severely immunocompromised PLHIV (302,305), data is extremely scarce for this group. As advised in the above mentioned joint statement, "immune suppression, indicated by a low CD4 (<200 cells/µL), or not receiving ART, should be considered a risk factor for severe COVID-19] [...] For PLWH with low CD4 counts (<200 cells/µL), or who experience a CD4 decline during a COVID-19 infection, remember to initiate opportunistic infection (OI) prophylaxis. This is not aiming at preventing a more severe course of COVID-19 but rather complications through additional OIs".

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**Breastfeeding:** Large organizations like WHO, RCOG and ACOG support the practice of breastfeeding even in the context of active SARS-CoV-2 disease, provided hygienic measures are applied (294,298).

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**Other special populations**

| Last update | HIV patients: The few available case-reports of SARS-CoV or MERS-CoV infection in patients with AIDS described mild disease symptoms and recovery (299,300). Similarly, for SARS-CoV-2, initial case reports and small uncontrolled case-series have suggested that the clinical spectrum and disease course of COVID-19 in people living with HIV (PLWH) is similar to that in HIV-negative persons (301–306). Similar conclusions are drawn from more recent matched case-control studies comparing HIV and non-HIV patients, albeit limited in size (307,308). These results and publications are mainly from Europe, USA and China. The largest study on PLWH in Europe to date is from a Spanish cohort of 77590 HIV positive persons under antiretroviral therapy (ART), among which 236 were diagnosed with PCR-confirmed COVID-19 between February and mid-April 2020. After standardization to the age and sex distribution of Spain, the risk in HIV-positive persons for COVID-19 diagnosis was 30/10 000 and 3.7/10 000 for COVID-19 death. In comparison, risk of COVID-19 diagnosis and death in the Spanish general population aged 20 to 79 years during the same period was 42/10 000 (33/10 000 when excluding healthcare workers) and 2.1/10 000, respectively. The risks of COVID-19 diagnosis, hospitalization, ICU admission, and death in the ART-receiving PLWH were greater in men and those older than 70 years, consistent with the age and sex-patterns reported for HIV-negative persons. Also, the risk for hospitalization was lower in patients receiving TDF/FTC (tenofovir disoproxil fumarate /emtricitabine) based ART versus those receiving other regimens, a result warranting further investigation due to possible confounders, particularly co-morbidities, not captured in the study (309). In a population cohort study from the Western Cape Province of South Africa, in adjusted analysis, HIV increased the risk of COVID-19 mortality by a factor of 2.14 (95% CI [1.70; 2.70]), with similar risks across strata of viral load and immunosuppression. Current and previous tuberculosis also increased COVID-19 mortality risk (adjusted hazard ratio: 2.70 [1.81; 4.04] and 1.51 [1.18; 1.93] respectively). Authors concluded that, although the HIV-associated risk of COVID-19 death may be over-estimated due to residual confounding (co-morbidities, socio-economic status), people with HIV should be considered as a high-risk group for COVID-19 management. Of note, if the larger prevalence of HIV in Africa permits such studies with higher participant numbers, results may not be transposable to Europe, due to multiple differences in population characteristics (310). Overall, as expressed in the recent joint statement of the BHIVA, DAIG, EACS, GESIDA & Polish Scientific AIDS Society "Whether or not PLWH on treatment with a normal CD4 count and suppressed VL (viral load) are at an increased risk of serious illness or death, many will have other conditions that increase their risk. Indeed, almost half PLWH in Europe are older than 50 years and chronic medical conditions, including cardiovascular and chronic lung disease, are more common in PLWH". This is supported by a study of the multi-center research network TriNETX (USA), comparing 404 PLWH and 49763 non-HIV with COVID-19 diagnosis (patients>10y). If crude COVID-19 mortality was higher in PLWH, propensity matched analyses revealed no difference in outcomes, indicating that the higher mortality was driven by the higher burden of co-morbidities (311). Importantly, although mild presentation and recovery from COVID-19 severe disease has been described in severely immunocompromised PLHIV (302,305), data is extremely scarce for this group. As advised in the above mentioned joint statement, "immune suppression, indicated by a low CD4 (<200 cells/µL), or not receiving ART, should be considered a risk factor for severe COVID-19] [...] For PLWH with low CD4 counts (<200 cells/µL), or who experience a CD4 decline during a COVID-19 infection, remember to initiate opportunistic infection (OI) prophylaxis. This is not aiming at preventing a more severe course of COVID-19 but rather complications through additional OIs".

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**Last update**

4 September 2020
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 (312,313).

**Cancer patients:** Systematic reviews and meta-analysis of published reports until end April show a pooled prevalence of cancer in COVID-19 patients of 2-3.5% and a higher risk of severe disease and mortality in patients with cancer versus without cancer (314–317). Most frequent cancer types reported among COVID-19 hospitalized patients are lung, breast, gastrointestinal, genitourinary, prostate and hematological (318–323). Case-fatality rate (CFR) in cancer patients with COVID-19 ranges between 11% to 32% (318–324). In addition, studies have shown that patients with hematological malignancies (CFR of 37-41%) have poorer prognosis than those with solid tumors (CFR of 17-25%) (320,324). Among solid cancer patients, patients with lung cancer have been shown to have the highest death rate and highest frequency of severe events (323). In Belgium, a population-based analysis showed that 8.7% of hospitalized COVID-19 patients were patients with a solid tumor and that the 30-day in-hospital mortality was higher compared to patients without cancer (31.7% vs 20%) (325). The effect was more pronounced in younger patients (<60 years) and patients without co-morbidities. Risk factors of death were investigated in cancer patients and include, as also described in the general COVID-19 population, older age, male sex, smoking status and number of co-morbidities but also a more advanced Eastern Cooperative Oncology Group (ECOG) performance status and active cancer (316,322).

Two larger studies on COVID-19 in patients with hematological malignancies have been conducted (326,327). Both studies demonstrate a higher mortality in COVID-19 patients with hematological malignancy compared to those without. The most common hematological malignancies were Non-Hodgkin lymphoma, myeloid neoplasms and plasma cell neoplasms. Older age, type of malignancy (acute myeloid leukemia, indolent non-Hodgkin lymphoma, aggressive non-Hodgkin lymphoma, or plasma cell neoplasms), disease status, and the severity of COVID-19 were associated with worse overall survival while time since hematological malignancy diagnosis or last anticancer treatment were not (326). All these results indicate that certain subgroups of cancer patients (solid and hematological) should be regarded as a vulnerable population for COVID-19. Studies on impact of anticancer therapy on COVID-19 outcome give conflicting data. Several studies describe that receiving chemotherapy within 4 weeks, other therapies (radiotherapy, immunotherapy, targeted therapy) or surgery had no effect on mortality from COVID-19 disease (321–324,328). On the other hand, Yang et al. describes chemotherapy as a risk factor for in-hospital death (320). Receiving radiotherapy was also suggested to be associated with increased mortality (329). The study from Dai et al. suggests that patients with surgery or immunotherapy have a higher death rate (323). A significant limitation of these studies are the small number of patients. Caution is needed to make recommendations based on limited evidence. General and cancer type specific recommendations for patient care are available at the ESMO website (https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic).
following EMA evaluation, the European Commission has granted a conditional marketing authorization for remdesivir for the treatment of COVID-19 in adults and adolescents from 12 years of age (with at least a body weight of 40kg) with pneumonia who require supplemental oxygen. Following the Belgian recommendations, its use may be considered in such patients, taking into account a series of precautions detailed in the guidance. Use of the other cited drugs should be limited within ongoing registered clinical trials.

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 (331,332). 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 (333,334). 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 (335), (iv) the knowledge that patients with these conditions are frequently treated with ACEi and ARBs (336). However, various counter-arguments to this hypothesis have been advanced (337), and there is currently no evidence from clinical or epidemiological studies that establishes a link between their use and severe COVID 19 (338,339).

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” (340). Belgian treatment guidelines currently state “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].

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