**FACT SHEET**
**COVID-19 disease (SARS-CoV-2 virus)**

15 July 2021, VERSION 11

**Disclaimer:**
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Over 145,000 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and at the speed with which discoveries are being made, certain references included are preprint papers that have not yet been peer-reviewed.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 10 (31 May 2021)
FACT SHEET
COVID-19 disease (SARS-CoV-2 virus)

15 July 2021, VERSION 1

Pathogen

| Virology | Taxonomy: COVID-19 is caused by the virus SARS-CoV-2. This virus belongs to the Coronaviridae family, in the Nidovirales order. The subgroups of the coronavirus family are alpha (α), beta (β), gamma (γ), and delta (δ) coronavirus. The four ‘common human coronaviruses’ are 229E (α coronavirus), NL63 (α coronavirus), OC43 (β coronavirus) and HKU1 (β coronavirus).
| Last update | 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).
| 4 September 2020 | 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.

![Figure 1. Structure of respiratory syndrome causing human coronavirus (2)](image_url)

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). Data indicate that the priming of its S protein for membrane fusion involves the protease TMPRSS2 (4). Fusion ultimately results in the release of the viral RNA genome into the cell cytoplasm. Based on knowledge from SARS-CoV and other coronaviruses, the next steps leading to viral replication would involve viral RNA translation, assembly of viral replicase transcription complexes, viral RNA synthesis, assembly of virions within the endoplasmic reticulum–golgi intermediate compartment, and transport of these to the cell surface inside vesicles. The newly formed infectious virions are then released from the host cell by exocytosis (3).

Genetic diversity & viral variants

| Genetic diversity & viral 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 rose in frequency due to natural selection of favourable mutations, random genetic drift, or epidemiological factors. New variants are classified according the potential impact on transmissibility, severity and/or immunity that is likely to have an impact on the epidemiological situation. ECDC classifies variants as ‘Variants of Concern’ (VOC) if the impact is known to be significant, ‘Variants of Interest’ (VOI) if preliminary evidence is indicating a potential impact, and ‘Variants under Monitoring’ if the evidence is still |
| Last update | 12 May 2021 |
weak. Updates on the distribution of variants in Belgium is available on the [NRC website](https://www.nrc.org), in Europe on the [ECDC website](https://www.ecdc.europa.eu), and in the world on the [WHO website](https://www.who.int).

**D614G variant.** Till beginning 2021, the main circulating variant of SARS-CoV-2 was the D614G variant (also referred to as G614), resulting from a D-to-G amino acid change caused by a single nucleotide mutation at position 1841 of the S-gen in the Wuhan reference strain (D614). Initially originating in China, this variant emerged in Europe, and went on to become the globally dominant strain over the course of three months (5): as SARS-CoV-2 is transmitted more rapidly than it evolves, the viral population is becoming more homogeneous.

Based on CT-value analysis, it had been suggested that the G614 variant is associated with potentially higher viral loads but not with disease severity (6). Nevertheless, higher viral loads do not prove per se an increased transmission potential, and there was debate whether G614 was more infectious than D614, as nicely summarized by Grubaugh et al (7). Later studies demonstrated, however, shifts over time versus the G614 variant in the same geographic areas, providing more arguments for a higher transmission rate of this variant (8,9). Both these studies did not find any evidence of a significant relationship between virus genotypes and altered virulence. A study ex vivo and in vivo in rodents concluded that the D614G substitution enhanced SARS-CoV-2 infectivity, competitive fitness, and transmission in primary human cells and animal models (10).

Although the G614 mutation is located in the S protein, it appeared 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 18,514 sequences, also concluded that a vaccine candidate based on the Wuhan reference strain was likely to be efficacious against all lineages circulating at that time (11). However, it still remained 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 (6).

**Alpha variant.** In November 2020, a new SARS-CoV-2 variant (VOC202012/01, later named 501Y.V1, lineage B.1.1.7, initially referred to as the ‘UK variant’, but now referred to as the Alpha variant), was identified in the United Kingdom (12,13). The variant is defined by 14 mutations resulting in amino acid changes and three deletions, some of which influence the virus’s transmissibility in humans. In December 2020, the UK’s New and Emerging Respiratory Virus Threats Advisory Group reported that the rate of transmission of the variant was 71%, higher than for other variants, and that it may also have a higher viral load (14). Mathematical modelling showed that an assumed 56% higher transmissibility is likely to lead to a large increase in incidence, with hospitalizations and deaths projected to reach higher levels in 2021 than were observed in 2020, even if stringent restrictions were maintained (15). A later modelling study established that the variant spread during the English lockdown (from November 5 to December 2) with an average R=1.25, against 0.85 for other variants (16), and another study that it was 75% more transmissible than other variants (17). A Danish modelling study from Denmark, on the other hand, estimated an additional transmissibility of 36% (18). A study in Canada found that the secondary attack rate was 1.31 times higher than for non-VOC cases (19). A rapid scoping review in pre-print found reported increases of risk of transmission ranging from 45% to 71% (20). The consensus is that it is a bout 50% more transmissible than previous variants.

One of the changes with an impact on the amino acid sequence of the Alpha variant is a deletion at position 69/70 of the Spike-protein, which has been found to affect the performance of some diagnostic PCR assays that use an S gene target (TaqPath assay). By 20 December 2020 more than 97% of PCR tests in England which test negative on the S-gene target and positive on other targets were due to the 501Y.V1 variant. S gene drop-out has therefore been used as a proxy for 501Y.V1 (21). Analysis of data in the UK, as of January 10, 2021, found that the secondary attack rates for cases with S gene deletion were 25% to 40% higher than for cases without S-gene deletion (22).

Initial assessment by Public Health England of disease severity through a matched case-control study reported no significant difference in the risk of hospitalisation or death compared to other variants (23). Later studies confirmed, however, an increased risk in both hospital admission and death (24).
A study coordinated by the ECDC compared the hospitalisation rate of the B.1.1.7 variant to the rate among non-variants. The study included 19,207 cases of SARS-CoV-2 variant B.1.1.7/S gene target failure from 7 European countries and found an adjusted odds ratio for hospitalisation of 1.7 (95% CI: 1.0 – 2.9) and for intensive care admission of 2.3 (95%CI:1.4 – 3.5) (25). The risk increase was highest in the age group 20-60 years, which confirms reports from hospitals that the variant is particularly more severe among relatively younger people.

Initially, there was concern that children are, relatively compared to adults, more susceptible to the variant. A later technical brief of Public Health England, however, did not find any significant differences in age distribution by S gene detection (as a proxy for 501Y.V1) (26). Real life vaccine effectiveness (VE) data are reassuring in terms of the effectiveness of both Comirnaty® (Pfizer-BioNTech) and Vaxzevria® (AstraZeneca-Oxford) against the Alpha variant (27–37). For Spikevax® (Moderna) real life effectiveness data are less available, but a Canadian pre-print showed evidence of good protection of SpikeVax® (37) and a US preprint found good protection of either Comirnaty® or Spikevax® (no distinction made between two types of vaccine) against infection during a time at which 69% of the circulating virus belonged to one of the following variants: B.1.1.7, B.1.427, B.1.429 (38). Additionally, a laboratory study suggests no significant reduction of antibody neutralization of COVID-19 vaccine Spikevax® elicited sera against the Alpha variant (39). Caution is however always needed when interpreting results of neutralization assays since correlates of protection have not been determined yet. Currently, no data are available for the COVID-19 Vaccine Janssen® (Johnson & Johnson).

The Alpha variant rapidly became the predominant variant in Europe and worldwide (40). In Belgium, baseline surveillance showed that the percentage of infections caused by it increased from 7.1% in the week of 4-10 January 2021 to 90.3% in the period between 3 May and 16 May (41). However, since then its share has declined due to the rise of the Delta variant (see below). In the week between 28 June and 11 July it represented only 28.1% of all infections.

An additional mutation (E484K - a mutation improving the ability of the virus to evade the host’s immune system) occurred in the B.1.1.7 variant and it is expected that this could lead to a reduced sensitivity to immunity induced by previous variants (42). The spread of this subtype (named B.1.17 with E484K) is, however, still limited. As of 11 July 2021, 52 cases had been detected in Belgium.

**Beta variant.** One of the mutations identified (N501Y) has also been reported in South Africa, where it arose independently of the Alpha variant (43). It is defined by eight mutations in the spike protein, including three substitutions (K417N, E484K and N501Y) at residues in its receptor-binding domain that may have functional importance. This variant, named 501Y.V2, lineage B.1.351, initially referred to as the ‘South Africa variant’ but now referred to as the Beta variant, has been reported from a total of 95 countries, but became only predominant in Southern Africa. In Belgium, the proportion of the Beta variant in the baseline surveillance initially increased to 7%, but then decreased. It was detected in only 0.5% of the samples in the period of 28 June-11 July 2021. The decrease is probably a result of the sharp increase of initially the Alpha variant, and later the Delta variant.

Preliminary results, using a mathematical model estimated that 501Y.V2 is 50% (95%CI: 20-113%) more transmissible than previously circulating variants in South Africa (44). However, the more rapid spread could also be partially due to the reduced neutralisation by antibodies. Laboratory studies of a limited number of patients from South Africa showed indeed that the variant is less susceptible to antibody neutralization by COVID-19 donor plasma, raising concerns of a possible increased rate of SARS-CoV-2 re-infections (45,46).

The above mentioned study coordinated by the ECDC, included 436 B.1.351 cases and found an adjusted odds ratio for hospitalisation of 3.6 (95% CI: 2.1 – 6.2) and for intensive care admission of 3.3 (95% CI:1.9 – 5.7) compared to non-variant cases (25). This appears to indicate that the variant causes more severe disease.

The Beta variant also poses somewhat greater challenges on vaccine effectiveness due to the presence of the E484K escape mutation. Data from Qatar show that VE ≥ 14 days after the second dose of Comirnaty® against infection with the Beta variant was about 15% lower as compared to the
Alpha variant. However, substantial VE (75%; 95% CI: 70.5-78.9) was still achieved. Moreover, VE against severe infections was high (100.0%; 95% CI: 73.7–100.0) and in line with that against the Alpha variant (100.0%; 95% CI: 81.7–100.0) for the two-dose regimen. However, one dose did not offer protection against severe infections with the Beta variant (as compared to a VE of 54.1% (95% CI: 26.1–71.9) for the Alpha variant) (35,47), emphasizing the necessity of the second dose. In addition, an Israeli pre-print found that breakthrough cases were disproportionately infected with B.1.351 as compared to non-vaccinated cases (odds ratio 8:1), suggesting a possible reduced vaccine effectiveness. Although the authors note that all these cases arose 7–13 days after the second dose with no breakthrough case arising after that (possibly indicating only a short time window after full vaccination during which this reduced effectiveness occurs) (48), this does however not correspond to what was found in the Qatar study, in which lower effectiveness was also seen ≥ 14 after the second dose (35). Several laboratory studies also suggest a reduction in neutralizing capacity against the Beta variant of Comirnaty® or Spikevax® elicited antibodies (39,49–54). In contrast, according to a Pfizer press release, Comirnaty® was 100% effective in preventing COVID-19 cases in South Africa, where the B.1.351 lineage was prevalent (https://www.pfizer.com/news/press-release-detail/pfizer-and-biontech-confirm-high-efficacy-and-no-serious), but these results have not yet been published. A Canadian pre-print showed only minor reductions of 1 (and 2 doses, data for Comirnaty® only) of Comirnaty® and Spikevax® in protection against symptomatic infection with the Beta and Gamma variant as compared to the Alpha variant. No reduction in protection against hospitalisation or death was observed. However, it is important to note that in this study, Beta and Gamma variants are taken together as one group, so it is impossible to distinguish both (37). A South African study found a very low effectiveness 10.6% (95% CI: 66.4 to 52.2) of two doses of Vaxzевria® against mild to moderate laboratory confirmed COVID-19. No data on protection against severe disease or death were available (55). These results led to the South African decision to halt the vaccine roll-out of Vaxzевria®. It should be noted that the dose interval was 21-35 days, which is substantially lower than the 12 weeks used in Belgium, known to yield higher protection (56). In addition, two studies looking at antibody neutralization also found a substantial (9-fold) lower neutralizing capacity against the South African variant of Vaxzевria® elicited sera (52,57). In contrast, the above mentioned Canadian study shows 16% reduction in protection of 1 dose (no data for 2 dose available) of Vaxzевria® against symptomatic infection of the Beta and Gamma variant (VE 48%; 95% CI: 28-63) as compared to the Alpha variant (VE 64%; 95% CI: 60-68). Protection of 1 dose against hospitalisation or death was similar to that observed for the Alpha variant. However, as mentioned, Beta and Gamma variants were taken together as one group, so it is impossible to distinguish both (37). Limited data are available for the COVID-19 Vaccine Janssen®. According to the phase III J&J clinical trial, efficacy was lower in South Africa (with 95% of cases due to South African variant) than in the US between 14 and 28 days after administration of the second dose, mainly for moderate to severe critical infections (and to a lesser extent for severe critical infections only). After 28 days, efficacy reached more similar (albeit still slightly lower) levels (58). In addition, laboratory studies suggest a 3.6 to 5-fold reduction in neutralizing capacity of sera from J&J vaccinees (59,60), but CD8 and CD4 T cell responses seem to not be affected (60). Caution is however needed when interpreting results of neutralization assays since correlates of protection have not yet been determined and results should be confirmed with real-life effectiveness studies.

Gamma variant. In the beginning of January 2021, another variant with S:K417N, S:E484K and S:N501Y mutations (S01Y.V3 or variant P.1, lineage B.1.1.28) was detected in Japan in travellers arriving from Brazil (61). It was therefore initially referred to as the 'Brazilian variant', but is now referred to as the Gamma variant. The variant has been reported from 62 countries, but only became predominant in some South American countries. In Belgium, its proportion in the baseline surveillance samples has been fluctuating. In the period of 28 June-11 July 2021, it represented 6.3% of the baseline surveillance samples, and according a modelling exercise by the NRC it has 7% transmission advantage compared to the Alpha variant. Preliminary investigations in Brazil have shown a rapid increase in the proportion of cases raising similar concerns for potential increases in transmissibility or propensity for re-infection (62). A modelling study, using surveillance data from hospitalized patients in Manaus, estimated transmissibility to be 2.6 times higher than previous variants, ranking it as the most transmissible among the current identified SARS-CoV-2 VOCs (63).
Another modelling exercise estimated a 1.4-2.2 higher transmissibility and that it evades 25-61% of protective immunity arising from infection with previously circulating variants (64).

The study coordinated by the ECDC described above included 352 P.1 cases. Compared to non-variant cases, P.1 cases had an adjusted odds ratio for hospitalisations of 2.6 (95% CI: 1.4–4.8) and for intensive care admission of 2.2 (95% CI: 1.8–2.9), suggesting that also this variant causes a more severe disease pattern (25).

Although, according to an ECDC risk assessment, the presence of the E484K mutation (also present in the Beta variant) may indicate a profile similar to the Beta variant, some more reassuring preliminary data are coming in. As mentioned above, a Canadian pre-print showed only minor reductions of 1 dose (and 2 doses, data for Comirnaty® only) of Comirnaty® and Spikevax® in protection against symptomatic infection of the Beta and Gamma variant as compared to the Alpha variant, while a 16% reduction in protection of 1 dose (no data for 2 dose available) of VaxZevria was estimated. No reduction in protection against hospitalisation or death was observed for any of the 3 vaccines. However, as mentioned, Beta and Gamma variants are taken together as one group, so it is impossible to distinguish both (37). Two pre-prints of laboratory studies found only moderate reductions (2.6-4.8 fold) of antibody neutralizing capacity of Comirnaty®, Spikevax® or VaxZevria® elicited sera against the P.1 variant (52,65). In one of these studies, looking at Comirnaty® and VaxZevria®, the neutralizing capacity was in line with what was found against the Alpha variant and was substantially higher than that against the Beta variant (52). Limited data are available for the COVID-19 Vaccine Janssen®. According to the phase III J&J clinical trial, efficacy was very similar in Brazil as compared to the US. But at that time 69% of cases were due to Brazilian variant of interest P.2, and not the variant of concern P.1. Laboratory studies suggest a 3.3 to 3.6-fold reduction in neutralizing capacity of J&J vaccinees’ sera (59,60), but CD8 and CD4 T cell responses seem to not be affected (60). Caution is however needed when interpreting results of neutralization assays since correlates of protection have not yet been determined and results should be confirmed with real-life effectiveness studies.

**Delta variant.** This variant was first detected last year in India, and is a subtype of lineage B.1.617 (B.1.617.2), the other subtypes being B.1.617.1 (Kappa variant), and B.1.617.3 (66). It is sometimes referred to as a double mutation variant because it has mutations in the SARS-CoV-2 spike protein’s coding sequence at E484Q and L452R. It has, however, several mutations of interest within the S gene (including L452R, D614G, P681R and T478K). Subtypes B.1.617.1 and B.1.617.3 do not have the T478K mutation, but have an E484Q mutation. The Delta variant has rapidly spread first in India and then in the UK, at a faster rate than previous variants (67). It is rapidly increasing in several other countries (already reported by 79 countries) and was by the end of June 2021 already the most common variant in the UK and in Portugal. In Belgium, it became predominant at the beginning of July and represented in the period of 28 June-11 July 2021 already 62.6% of the baseline surveillance samples. The Kappa variant has till now been identified in 16 samples only.

The Delta variant is judged by Public Health England, with high confidence, to be 40-60% more transmissible as the Alpha variant, based on the growth rate, secondary attack rates and household transmission studies, and in-vitro increased replication in biological systems (68). An analysis of the global data submitted to GISAID, estimated the effective reproductive number for the Delta variant to be 55% (95%CI 43-68%) higher than the Alpha variant and 97% (95%CI 76-117%) higher relative to non-VOC/VOI (69,70). ECDC projects that 70% of new SARS-CoV-2 infections will be due to the Delta variant in the EU/EEA by early August and 90% by the end of August. Early evidence from England and Scotland suggests there may be an increased risk of hospitalisation compared to Alpha cases, but more evidence is needed.

Pseudovirus and live virus neutralisation using convalescent sera from first wave and Alpha infections showed a reduction in neutralisation. However, based on the available evidence ECDC concluded that emergence of the Delta VOC is not associated with an increase in reinfecions amongst recovered individuals infected with previously circulating SARS-CoV-2 strains and that although convalescent sera demonstrate reduced neutralisation capacity against the Delta VOC when compared to ancestral strains, they still effectively neutralise the Delta VOC in-vitro (69).
Indeed, Liu et al. showed that neutralization of the Delta variant by convalescent sera is reduced when compared with the Wuhan strains but they saw no evidence of widespread antibody escape. They did find that both B.1.351 and P.1 infected sera showed markedly more reduction in neutralization of B.1.617.2 suggesting that individuals previously infected by these variants may be more susceptible to reinfection by B.1.617.2 (71). Other laboratory evidence of functional evasion of naturally acquired immunity suggests a 4.6 to 6-fold reduction in neutralising titers (72,73). Results from the UK indicate that during the period that the Delta VOC became prevalent, reinfections remained at very low numbers in individuals previously either PCR positive or seropositive (74).

Based on the available evidence ECDC concludes that those who have only received the first dose of a two-dose vaccination course are less protected against infection with the Delta VOC than against other variants, regardless of the vaccine type. However, full vaccination provides nearly equivalent protection against the Delta VOC as for the Alpha VOC (69). Indeed, a UK pre-print found that with 2 doses of either Comirnaty® or Vaxzevria® there were only modest reductions in vaccine effectiveness against infection with the Delta variant as compared to the Alpha variant (Comirnaty®: 93.4% (95%CI: 90.4-95.5) vs. 87.9% (95%CI: 78.2-93.2); Vaxzevria®: 66.1% (95% CI: 54.0-75.0) vs. 59.8% (95%CI: 28.9-77.3)). Absolute differences in VE were bigger after only 1 dose (33.5% vs. 55.1% for both vaccines), again emphasizing the need for a second dose (75). Similar findings were done in a Scottish study, using S gene positivity as a proxy for the Delta variant and S gene negativity as a proxy for the Alpha variant. The authors estimated that 2 doses of Comirnaty® had a VE against infection of 92% (95% CI 90–93) for S gene-negative and 79% (95% CI: 75–82) for S gene-positive. Vaxzevria® showed a VE of 73% (95%CI: 66–78) and 60% (95% CI: 53–66), respectively (76). A UK study, on the other hand, found that VE against hospitalization with Delta, was similar to that seen with Alpha, both after 1 and after 2 doses. A VE of 94% (95%CI: 46-99) after 1 dose and 96% (95%CI: 86-99) after 2 doses of Comirnaty® for the Delta variant was estimated (versus respectively 83% (95%CI: 62-93) and 95% (95%CI: 78-99) for the Alpha variant). And a VE of 71% (95%CI: 51-83) after 1 dose and 92% (95%CI: 75-97) after 2 doses of Vaxzevria® for the Delta variant was estimated (versus respectively 76% (95%CI: 61-85) and 86% (95%CI: 53-96) for the Alpha variant) (77).

The above mentioned findings are very similar to those in a Canadian pre-print, though this study showed similar protection (as compared to the Alpha variant) of 1 dose of Vaxzevria® against symptomatic infection. And additionally, the study showed some (11%) reduction (as compared to the Alpha variant) in protection of 1 dose (no data for 2 dose available) of Spikevax® against symptomatic infection (37). Several laboratory studies have also shown sera from persons vaccinated with Spikevax® to have a modestly reduced (2.1-4-fold) neutralizing capacity against B.1.617.2 variant (78,79). No real life effectiveness data are available for the for the COVID-19 Vaccine Janssen®, but a pre-print of a laboratory study suggests a 1.6-fold reduction in neutralizing capacity, which is a lower reduction as compared to both the Beta and the Gamma variant (59).

Other Variants. Another variant, characterized by the S131I, W152C mutations in the NTD and by the L452R mutation in the RBD (B.1.427/B.1.429), originated in California in May 2020 and is called the Epsilon variant. The fast rise in their number, with an estimated 20% increased transmission, and evidence of reduced neutralization by convalescent and post-vaccination sera (80,81) led initially to their classification as a VOC by the US CDC. However, is has meanwhile been reclassified as a variant of interest (VOI) due to the significant decrease in the proportion nationally and available data indicating that vaccines and treatments are effective against this variant (82). The variant is mostly limited to the US and only one case has been detected in Belgium, where it is no longer considered a VOI. Limited real-life effectiveness data are available at this stage, but one US preprint found good protection of Comirnaty® or Spikevax® (no distinction made between two types of vaccine) during a time at which 69% of the circulating virus belonged to one of the following variants: B.1.1.7, B.1.427, or B.1.429 (38). On the other hand, several pre-prints of laboratory studies found minor to
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| Reservoir | Like for previous invasive coronaviruses, such as SARS- or MERS-CoV, SARS-CoV-2 is believed to have a zoonotic origin and to result from a cross-species transmission. Whole genome sequencing has shown that SARS-CoV-2 is 96.2% identical to a bat coronavirus (Bat CoV RaTG13). This suggests that bat CoV and human SARS-CoV-2 might share the same ancestor, and that bats are a possible reservoir for the virus (1). Additional phylogenic studies are in favor of this hypothesis (85–87).

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 (88). 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 (89). Various wild mammals, as well as cats and dogs, also have ACE2 configuration that is predicted to bind with SARS-CoV-2 S protein (90,91).

A major concern is the potential formation of a non-human reservoir from where the viruses could be reintroduced once circulation of SARS-CoV-2 in humans is suppressed or even stopped. Mink farms form such a potential reservoir. Spillover of SARS-CoV-2 from humans to mink and minks to humans was first reported in the Netherlands, and later also in Spain, Italy, the USA, Sweden and Greece (92). In Denmark, the Danish National Institute of Public Health found that viruses had spilled back from mink farms into the community, and that during the passage through mink the virus had accumulated mutations in the spike protein gene (93). Some of the mutations observed in the viral genome sequences taken from Danish and Dutch mink farms are suggestive of adaptation of the virus to this new host (94). In response, both the Netherlands and Denmark have culled all minks in the country.

| Physical and chemical resistance of the virus | In the absence of any ventilation, according to a study (95), 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 (96).

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, peroxycetic acid and chloroform (96,97).

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 (98) and the

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**Prevention**

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**General public**

For the general public, **handwashing, social distancing and wearing of a face mask are the recommended measures to protect oneself**. Keeping a distance of at least 1m means that droplets from a normally breathing person will not reach you (102) and has been shown in a meta-analysis to be associated with a lower risk of viral transmission (103).

**Community Masks**

Because of the possibility of asymptomatic and especially pre-symptomatic transmission face masks are now universally recommended, mainly as source control, i.e. 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 (104). Modeling data for Influenza suggest that population-wide use of masks could importantly reduce spread of the virus (105–107). The filtration capacity of home-made masks is lower than that of medical/surgical masks, but they do offer outward protection, despite imperfect fit or adherence (108–114).

Important public health authorities like CDC and Robert Koch Institute started advising wearing of home-made masks for the population from April 2020 onwards, in addition to social distancing measures and strict hand hygiene (115,116). ECDC listed a number of potential risks and benefits without either recommending or discouraging the use (117). A highly-influential review of the evidence compiled on April 10th by a consortium of scientists not only concluded that there is evidence on the efficiency of cloth masks but also that, based on experience with other preventive measures, the claim that their use would lead to increased risk behavior and less observance of other measures is unfounded (118). In contrast, a French study found that in a computer-based experiment, participants allowed persons who were wearing a face mask to come closer than unmasked persons (119). WHO, after reviewing all the evidence, still recommended against the use of community masks on April 6th but changed their position on the 5th of June. However, they still recommend mask wearing should be part of a comprehensive package of measures, including social distancing, and that it is insufficient as a single measure (120). WHO further states that masks should never be used during exercise and by children under 6 years of age. For children between 6-11 years, a risk-based approach should be taken, accounting for both potential risks and benefits (121). Lab-based experiments clearly show that the effectiveness of masks is greatest if they are worn by both the index case and the contact, and that even cotton masks can importantly lower the amount of virus that is transmitted (114) as well as offer some protection against particles in the aerosol-range (0.05µm) (122). However, we need to continue to bear in mind that the real-world efficiency of masks will be determined by many factors, such as intensity of virus circulation, compliance with other measures (like social distancing and hand hygiene) and the correct use and quality of the mask. It is therefore not surprising that a randomized-controlled trial from Denmark did not show any additional benefit of mask-wearing as individual protection (i.e. at a time of strict social distancing and without mask use by the source patient) (123) or that mask-wearing by the contact was not found to be protective in a contact tracing study from Singapore (i.e. during prolonged, close exposure) (124). Practical recommendations on the use of masks in the community for Belgium can be found here ([NL/FR]).

**Personal Protective Equipment**

**Healthcare workers**

WHO recommends the use of a **surgical mask, gown, gloves, and goggles or face shield** for healthcare workers coming into close contact (<1.5m) with possible or confirmed cases of COVID-19 (125). During the SARS epidemic, adherence to these precautions was found to be effective to avoid infection in healthcare workers. The effect was largest for hand hygiene and use of masks (126).

**Surgical Masks vs. FFP2**

Different health care authorities have issued different advice on the recommended PPE (127), 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

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USA (99) and using dry heat (30’ at 65-70°C) in Germany (100). 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 (101).
In the above-mentioned trial during the SARS epidemic (126), 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 (128,129). This conclusion was confirmed by a meta-analysis including six RCTs published in March 2020 by the Chinese Cochrane Center (130). 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 (131).

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 (103). 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 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 (132). Although meta-analysis of various trials still conclude that there is insufficient evidence to favour one type of mask over another in health-care settings (133) Belgian recommendations broadened the indications for use of FFP2-masks in view of rising concerns around airborne transmission, more transmissible variants and wider availability of FFP2-masks, applying the precautionary principle.

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 (134). In addition, a few studies reported an increased risk of SARS-CoV infection associated with tracheotomy, non-invasive 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 (135). 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: (127,136)

- 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).
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Different authorities list different procedures (137). 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 (132,134,136).

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The COVID-19 vaccines in use and in development apply various vaccine technology platforms. The main types include nucleic-acid vaccines (DNA and RNA), viral-vector vaccines (replicating and non-replicating), virus vaccines (attenuated or inactivated) and protein-based vaccines (virus-like particles, protein subunits) (138). According to the [WHO COVID-19 candidate vaccine landscape](https://www.who.int/emergencies/diseases/novel-coronavirus-2019/vaccines) (updated on 29 June 2021), 184 vaccines are in pre-clinical development and 105 vaccines are now in clinical development (62 in phase I or I/II, 16 in phase II or II/III, 19 in phase III clinical trials and 8 in phase IV).

Vaccines that have received conditional authorization by the EU Commission based on evaluation and scientific review by European Medicinal Agency (EMA) are those from [BioNTech-Pfizer](https://www.biontech-pfizer.com/) (mRNA vaccine; Comirnaty®), [Moderna](https://www.moderna.com/) (mRNA vaccine; Spikevax®), [AstraZeneca-Oxford](https://www.astrazeneca.com/) (non-replicating viral vector vaccine, ChAdOx1; Vaxzevria®) and [Johnson & Johnson](https://www.jnj.com/) (non-replicating viral vector, Ad26; COVID-19 Janssen vaccine®). Full updates and key documents can be found on the [EMA website](https://www.ema.europa.eu/en). All have demonstrated high vaccine efficacy (140–142). Other vaccines are currently in rolling-review.

In addition to the EMA-authorised vaccines, the [WHO emergency use list](https://www.who.int/emergencies/diseases/novel-coronavirus-2019/vaccines) includes the COVID-19 vaccines from Serum Institute of India (non-replicating viral vector vaccine, ChAdOx1-S; Covishield®), Sinovac (inactivated adjuvanted vaccine, Vero Cell; CoronaVac®) and BIBP/Sinopharm (inactivated adjuvanted vaccine, Vero Cell; COVID-19 Vaccine BIBP). Finally, the Gamaleya vaccine (viral-vector Ad26/rAd5 heterologous prime boost vaccine; Sputnik V (Gam-COVID-Vac)) (143), CanSino vaccine (viral vector Ad5), Vector Institute vaccine ("EpiVacCorona", protein-based) and the inactivated viral vaccines from Sinopharm-Wuhan and Bharat Biotech have received conditional or emergency use authorisations in some countries and are being deployed in national vaccine campaigns across the world ([NYTimes vaccine tracker](https://www.nytimes.com/2021/07/15/world/coronavirus-vaccines.html)).

According to the [WHO COVID-19 dashboard](https://covid19.who.int/), close to 3 billion COVID-19 vaccine doses have now been administered worldwide. The [ECDC vaccine tracker](https://ecdc.europa.eu/en/resources-publication/vaccine-tracker) gives an overview of vaccine roll-out in Europe.

Belgium’s vaccination campaign and roll-out officially began on the 5 January 2021, after an initial pilot phase end of December 2020. The vaccine campaign has used an approach by phases, targeting various priority groups (nursing home staff and residents, healthcare workers, residents of other residential collectivities, 65 year olds and above, persons with comorbidities, and more recently pregnant women) before it will be expanded to the general 18+ population. Comirnaty®, Spikevax® Vaxzevria® and Janssen’s COVID-19 Vaccine® are in use. The countries’ vaccine uptake and coverage can be followed on the national dashboard [epistat](https://epistat.snuhs.edu.tw/), and additional information can be found in our [FAQ surveillance](https://www.cdc.gov/coronavirus/2019-ncov/surveillance/faq.html) and [Vaccination page](https://www.cdc.gov/coronavirus/2019-ncov/vaccines/index.html).

**Vaccine effectiveness**

More promising results of vaccine effectiveness (VE) studies (set in “real-life settings” as opposed to clinical trials) are coming in, with results still mainly available for Comirnaty® (Pfizer-BioNTech) and Vaxzevria® (AstraZeneca-Oxford). In general, a good protection against infection (all or symptomatic) (28,30–32,36–38,144–159), hospitalization (27,28,30,37,145,150,154,158,160,161) and death (28,30,145,155,158,160) are found. Furthermore, a majority of these studies show substantial protection after the first dose, which further increases after the second dose (28,31–33,36–38,144–147,149,151,153,153–158,160).

One of the first large VE studies published was an Israeli study looking at VE after first and second dose of Comirnaty® against a range of different outcomes. It found that effectiveness 21–27 days after first dose was higher for severe outcomes than for milder outcome (severe disease 80% (95%
If VE has been found to decline mildly but significantly with age (149), several studies have shown that high effectiveness is still achieved in the elderly (27,28,30,33,145,161). The largest VE study published this far, found estimates in individuals of 85 years and older to be very similar to those in younger age groups (30). And in the above mentioned Israeli study, effectiveness against symptomatic COVID-19 in individuals of 70 years and older was slightly lower after the first dose but similar after the second dose, when compared to the general population (145). A Spanish study found VE against symptomatic COVID-19 was higher in people aged 18–59 years than in those aged ≥ 60 years, mainly for one dose (51%; 95% CI: 37 to 62, vs 30%; 95% CI: 10 to 45) and to a much lesser extent for two doses (84%; 95% CI: 74 to 90, vs 77%; 95% CI: 56 to 88), but differences were not statistically significant (154). In an English pre-print focusing on people ≥70 years old, very high effectiveness against symptomatic infection was achieved with both Comirnaty® and Vaxzevria®, with substantial additional lower risks for hospitalisation (>37%) and death (51%, but only results for Comirnaty® available) in those ≥80 years old with a positive test ≥14 days after the first dose (28). The above mentioned Scottish study, focussing on VE against hospitalisation of the first dose, found that effectiveness after the first dose in those ≥80 years was 81% (95% CI: 60–91) for Vaxzevria® and 88% (95% CI: 76–94) for Comirnaty® 28-34 days (27). However, some studies do report on substantially lower effectiveness in elderly. A Danish pre-print found close to no protective effect of one dose of Comirnaty® against laboratory confirmed SARS-CoV-2 infections in residents of long term care facilities (median age 84 years) or health care workers, with VE >7 days after second dose reaching 64% (95% CI: 14–84) in long term care facility residents and 90% (95% CI: 82–95) in health care workers. The authors suggest that the absence of a substantial protective effect after the first dose may be due to increased testing (and therefore increased detection of asymptomatic cases) (148). But other studies have found higher first dose VE despite incorporated data from regular testing schemes (34,36,144,147,151,153). Interestingly, in a pre-print, Shroti et al. did find that the protective effect of 1 dose of Comirnaty® or Vaxzevria® in residents of long term care facilities only appeared 28-34 days after vaccination, suggesting that in this frail population, protection may be achieved later than in the general population (34). A study of long term care facility residents of 65 years and older, found somewhat lower than generally observed protection against infection (71% 95% CI: 55.7–81.5) after 2 doses of an mRNA vaccine, but protection against hospitalisation (88.4% 95% CI: 74.9%–94.7%) and death (97.0%; 95% CI: 91.7%–98.9%) was still very high. Moreover, protection after 1 dose was 50-60% for all of the mentioned outcomes (158). In contrast, a Belgian pre-print found poor antibody responses in fully vaccinated, previously uninfected nursing home residents up to 49 days after the second dose whereas previously infected residents showed high antibody responses after vaccination. This suggest that perhaps adapted vaccination regimens are needed in this vulnerable population (163). Results from laboratory studies should be interpreted with caution though, since no correlate of protection has been defined yet.

In general, direct comparison of the referred articles is hard due to differences in test strategies, dosage schemes, vaccines, outcomes, time points, study populations and epidemic context.
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| **Asymptomatic disease:** Several studies have looked at vaccine effectiveness against asymptomatic infection and first results are promising. However, results at this stage are almost exclusively available for Comirnaty® and should always be interpreted with caution, as individuals asymptomatic at time of testing, may simply be pre-symptomatic and mild symptoms may go underreported. In a supplementary analysis, Dagan et al. report a 90% (95% CI: 83–94) effectiveness in prevention of asymptomatic cases of Comirnaty® ≥7 days after the second dose, but the authors themselves state having used absence of reported symptoms as an imperfect proxy for being (145). A similar imperfect approach was used by Haas et al. (asymptomatic defined as no reported fever or respiratory symptoms and no hospitalization or death due to COVID-19), resulting in 91.5% (95% CI: 90.7–92.2) effectiveness in prevention of asymptomatic cases of Comirnaty® ≥7 days after the second dose (30). In a study using data from screening pre-procedural patients, Tande et al. concluded that the risk of asymptomatic SARS-CoV-2 infection, as compared to unvaccinated individuals, was lower among those >10 days after the first dose (RR=0.21; 95% CI: 0.12–0.37) and among those >0 days after the second dose (RR=0.20; 95% CI: 0.09-0.44) of either Comirnaty® or Spikevax® (no distinction made between the two vaccines) (164). In addition, Mazagatos et al. found VE estimates against asymptomatic infection to be in line with the estimates against all infections (158). Recently two studies looked specifically at the incidence rate of asymptomatic infection in a population that underwent routine screening. Both studies had similar findings, with high protection against asymptomatic infection ≥7 days after the second dose of Comirnaty® (aIRR=0.10-0.14) (36,153). In addition, several studies (29,31,32,34,147–149) include asymptomatic cases in their estimates of effectiveness against laboratory confirmed SARS-CoV-2, but report no separate results for this outcome.

**Transmission:** First encouraging data on effectiveness of vaccination against transmission are coming in from the UK. A Scottish pre-print found that household members of healthcare workers vaccinated with at least one dose of Comirnaty® or Vaxzevria® had a lower risk of documented COVID-19 compared to household members of unvaccinated healthcare workers (hazard ratio: 0.70, 95% CI: 0.63–0.78) ≥14 days after first dose (150). An English study specifically looking at the risk of household transmission when the index case was vaccinated ≥21 days before testing positive, found that the likelihood of household transmission was 40-50% reduced. The effect was similar for both Comirnaty® and Vaxzevria®, and most index cases (93%) had received only one vaccine dose (165).

**Duration of vaccine induced protection:** Some laboratory data suggest that the immunity after vaccination may potentially be long lasting, but evidence is still limited. One study showed that high frequencies of S-binding germinal centre B cells and plasmablasts were sustained in draining lymph nodes for at least twelve weeks after the Comirnaty® booster immunization, enabling robust humoral immunity (166). And Johnson and Johnson reported on a sub-analysis of their Phase 1/2a trial showing results indicating that humoral and cellular immune responses were maintained until at least 8 months after vaccination. Results of these laboratory experiments should however be confirmed with effectiveness data (167). At the same time, several companies are investigating a third dose to boost immunity further.

**Mixed dose schedules:** Several EU countries have adopted a mixed dose schedule (or heterologous prime-boost schedule) as a result of a halt in or age restrictions of Vaxzevria® vaccination. However, at this stage limited data are available regarding these mixed dose schedules. Preliminary data found no important safety concerns (168–171) and the limited laboratory evidence available is suggestive of an at least equal immune response after a mixed dose schedule as compared to a homologous prime-boost schedule (168,169,171,172). However, evidence is limited and studies are often small, so these data should be confirmed in larger trials.

For more information on variants and effectiveness, see [Genetic diversity and Viral variants](#)

**Vaccine safety**
Phase III clinical trials allow the identification and characterisation of the common side-effects of each vaccine. These are benign, ranging from headaches to fever, and are summarized in the medicine’s agency AFMPS/FAGG FAQ.

In addition, to ensure the detection of rarer or late-onset adverse effects, post-marketing surveillance of vaccine safety is organized, both at national level (AFMPS/FAGG) and European level (EMA). Belgium’s national vaccine-safety data is available in a weekly bulletin published on the medicine’s agency AFMPS/FAGG website and EMA publishes monthly reports on vaccine safety profiles. Here we summarise the key safety signals and side-effects that have been identified through post-marketing surveillance.

Thrombosis with Thrombocytopenia Syndrome (TTS) is a newly identified syndrome classified by EMA as a very rare side effect for both Vaxzevria® and COVID-19 Vaccine Janssen®. The syndrome associates thrombo-embolic diseases of large vessels (including venous thrombosis of rare sites such as central venous sinus thrombosis (CVST) and splachnic vein thrombosis, but also arterial vein thrombosis) and thrombocytopenia. The reported cases have occurred within the first three weeks following vaccination. The majority of cases have been reported in women under 60 years of age, although biases such as underreporting in older age groups or increased exposure of women related to vaccine target populations are possible. EMA has published a benefit-risk model for Vaxzevria® with regards to TTS, and a visual risk contextualisation document. The overall case fatality rate of TTS, according to the most recent weekly UK MHRA report, is 18%. According to the same report, data so far shows a significantly lower incidence of TTS in the younger recipients after the second dose compared to the first dose. The exact physiopathology behind this syndrome is yet to be confirmed, but one of the leading hypotheses is that of an atypical heparin-induced thrombocytopenia-like syndrome, involving the production of platelet-activating anti-PF4 antibodies (173,174). Healthcare professionals should be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia and inform vaccinated people. Clinical and laboratory characteristics of such cases have been described in case series (146,147). Diagnostic work-up and management of such cases has been proposed by the Belgian Society on Thrombosis and Hemostasis. The guidance emphasises that prior thrombosis, risk factors of thrombosis and of cardiovascular diseases, and/or anticoagulant therapy are not identified as risk factors of TTS, and therefore do not represent a contraindication for vaccination.

Although still very rare events, severe allergic reactions (anaphylaxis) have occurred with Comirnaty® and Spikevax® at a higher rate than predicted by clinical trials or than what is usually observed with non-COVID vaccines. According to MMWR reports, anaphylactic reactions have been reported at a frequency of 11.1 cases per million doses with Comirnaty® (175) and 2.5 cases per million doses with Spikevax®. The lipid nanoparticles (polyethylene glycol (PEG) or “macrogols”) that coat the mRNA are believed to be implicated in the immunopathogenesis of these reactions. PEGs are known allergens which are commonly found in many household products, cosmetic, and medicines. Cases of anaphylaxis have also been reported with Vaxzevria®, however rates appear to be in line with those of non-COVID vaccines (Greenbook). Vaxzevria® does not contain PEGs but does contain the related compound polysorbate 80. A pragmatic document to assess allerg risk and management in potential vaccine recipients, taking history of allergy and other risk factors into consideration, is published on Belgium’s Superior Health Council website.

Capillary leak syndrome, a rare and severe disorder characterised by massive leakage of plasma from blood vessels into adjacent body tissues, has been identified as a very rare side effect of Vaxzevria®, which is now contraindicated in persons with a history of capillary leak syndrome. By end of May 2021, 14 cases had been reported from the EU/EEA and UK, where in total more than 78 million doses of Vaxzevria® had been administered. More information in the latest EMA safety report.

On the 9th July, EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) concluded that myocarditis and pericarditis can occur in very rare cases following vaccination with Comirnaty® and Spikevax®, with cases occurring primarily within 14 days after vaccination and more often after the second dose and in younger adult men. These conclusions are in line with those of the CDC’s Advisory Committee on Immunization Practices (ACIP), based of the cases reported by the United States.
These cases are reviewed in a MMWR report: As of June 11 2021, approximately 296 million doses of mRNA COVID-19 vaccines had been administered in the United States, and 1,226 reports of myocarditis after mRNA vaccination had been received. Median age was 26 years (range = 12–94 years), with median symptom onset interval of 3 days after vaccination (range = 0–179). Among 1,094 patients with number of vaccine doses received reported, 76% occurred after receipt of dose 2 of an mRNA vaccine. The highest reporting rates were among males aged 12–17 years and those aged 18–24 years. Acute clinical courses were generally mild; among 304 hospitalized patients with known clinical outcomes, 95% had been discharged at time of the review. Follow-up is ongoing to identify and understand longer-term outcomes after myocarditis occurring after COVID-19 vaccination (176).

Pregnancy and breast-feeding

Pregnancy and breastfeeding are not contraindications to COVID-19 vaccination. In May 2021, Belgium’s Superior Health Council updated its recommendations for the use of mRNA vaccines in pregnant women. In these recommendations, vaccination of pregnant women was no longer limited to certain groups (e.g., health care workers at high risk of exposure and women with co-morbidities that place them in a high-risk group for severe COVID-19), but advised for all. Pregnant women thereafter became a new priority group for vaccination in the country.

Adolescents & Children

End of May 2021, Comirnaty’s EU authorisation for use was extended to include children aged 12 to 15. The other EMA authorised vaccines are not currently recommended for use in children. Since July 7th 2021, vaccination in Belgium is open to all 12-15y olds on a voluntary basis, provided they have parental consent (or consent from their legal guardian).

Adolescents (12-17y): Pfizer-BioNTech reported favourable results of a Phase 3 trial in adolescents 12 to 15 years of age in a press-release. Health Canada has authorized use of Pfizer-BioNTech vaccine in adolescents aged 12 to 15 years (5 May 2021), whilst application to extend authorization to 12-15 year olds has been submitted to both FDA and EMA, with decisions expected mid-May and June respectively. Moderna has finished enrolling in a Phase II/III trial TeenCove, and completion estimated for June 2021. Encouraging primary analysis results were recently reported in a press-release.

Children (0-11y): Moderna announced on March 16 the start of its KidCOVE clinical trial, a Phase 2/3 study of the immunogenicity and safety of Spikevax® in children under 12 years of age. As for Pfizer-BioNTech, on March 25 they began their Phase I pediatric study, which will include 144 participants, and whose objective is to identify the preferred dosage level of the vaccine for three age groups - between 6 months and 2 years, between 2 and 5 years, and between 5 and 11 years.

**Ventilation**

*Last update 14 December 2020*

**Increased ventilation has been shown to reduce airborne transmission** (177). In addition to increased ventilation, experts recommend limited room occupancy, avoidance of air recirculation (use ‘extraction mode when using air conditioning) and frequent breaks (178–182). If recirculation of air is necessary, HEPA filters or MERV13 can filter sufficiently small particles (179). Two-and-a-half air changes have been reported to eliminate 90% of airborne contaminants (183). Opening doors and windows can generate around 5-17 air changes per hour (ACH), but this is highly dependent on several conditions (surface of the windows, orientation, outdoor temperature and wind speed...) (177,184).

Use of a CO₂-sensor can help to assess whether ventilation is adequate or not. CO₂-levels should be kept below 800-1000ppm (185). This usually corresponds to the ventilation threshold set by WHO of 10 l/s/person (186). Technical guidance for maintenance of ventilation systems are available on the website of the Federation of European Heating, Ventilation and Air Conditioning Associations and the Belgian Superior Health Council also issued advice on the topic.

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.
**Clinical Aspects**

**Modes of transmission**

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Evidence indicates that SARS-CoV-2 is transmitted from human to human by infectious droplets (194). 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 (195,196).

Transmission may also occur indirectly through contaminated surfaces or fomites, although that the risk is generally considered to be low (197). Several studies have shown extensive contamination of inanimate surfaces around an infected person (198) and other respiratory illnesses and coronaviruses can spread through indirect contact (186). However, epidemiological data and several studies of environmental transmission factors, showed that surface transmission is not the main route by which SARS-CoV-2 spreads (199,200). In most situations, cleaning surfaces using soap or detergent, and not disinfecting, is enough to reduce risk. Disinfection is generally only recommended in indoor community settings where there has been a suspected or confirmed case of COVID-19 within the last 24 hours (197,201).

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 (202–204). Especially in faeces, viral RNA seems to be present later and persists longer than in samples from the upper respiratory tract (205). **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 (202,206,207) but no cases of faeco-oral transmission have been documented (201). Finally, although in limited number, PCR-positive conjunctivals wabs have been reported in COVID-19 patients, with or without ocular symptoms (e.g., conjunctivitis), indicating a potential route of transmission via the ocular mucosa (208). 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’.

The potential of **long-range airborne transmission** of SARS-CoV-2 is no longer disputed, although its relative importance remains unclear. An evidence summary identified 8 studies in which air samples...
were taken in hospitals to detect SARS-CoV-2 (209). 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 (210) and unclear in another (211). In the third study (212), 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 (213,214) and previous experience with SARS (215–217). 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) (218), in fitness centres during Zumba classes (219), during a choir rehearsal (220), in a restaurant without fresh air supply but air being recirculated by the air conditioning (221) or among Chinese bus passengers (222). Reassuringly, all these outbreaks involve prolonged exposure in poorly ventilated areas. One study measured the amount of aerosol particles emitted by breathing, talking and singing and found that singing and loud talking emitted about 3 times more particles than breathing, and loud singing about 5 times more (223).

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

**Incubation period**

*Last update 9 July 2021*

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 (224–226). 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 (227). A modelling study by UHasselt used outbreak data from clusters in Singapore and Tianjin, China and found a mean generation interval (the time between 1 person being infected and that person infecting someone else) of 5.20 days for Singapore and 3.95 days for Tianjin (228). A rapid review of 40 studies found a median serial interval ranging from 1.0 to 6.0 days (based on 15 estimates) (229) and a meta-analysis of 11 studies calculated a pooled estimate of 5.4 days (230).

Larger studies and meta-analysis have since been carried out, and confirm a median incubation period ranging between 5 and 6 days (231,232). In a study by Yang et al analyzing 178 cases and 131 transmission chains in Hubei province, 95% of symptomatic cases developed symptoms with in 137 days (95% CI 12.5–14.9) of infection, and 99% within 17.8 days (95% CI 15.9–19.7] (231).

**Contagious period**

*Last update 9 July 2021*

**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 (233–240). A 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 (241).

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 (218,242–244). 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 (245).

Throughout the epidemic, evidence of pre-symptomatic transmission has accumulated (236,242,245–248). 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-infectee) 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 (249). 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 (239). A pre-print systematic review and meta-analysis of 17 studies calculated that the mean transmission time ranged from 2.91 days before symptom onset to 1.20 days after symptom onset, with a mean of 0.6 days before symptom onset (8). The authors conclude that transmission of SARS-CoV-2 is most likely in the day before symptom onset, although that in some contexts the mean could be almost three days before onset.

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 (250). In South Korea, a large outbreak occurred among fitness instructors and attendees where the index patient developed symptoms only 3 days after the workshop (219).

There is still uncertainty about the exact 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 (251). The proportion assumed by He et al and UHasselt lie within this range (44% and 48%, respectively). A model using data from a meta-analysis, estimated that 59% of all transmission comes from asymptomatic transmission, comprising 35% from pre-symptomatic individuals and 24% from individuals who never develop symptoms (252). 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 (250). 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 (227).

Currently, international guidelines (ECDC, WHO) and most country guidelines, including Belgium's, consider all potential contacts of a case from 48h before symptom onset.

End of contagious period:

- Data is available from contact tracing studies, modelling of transmission and studies using viral culture. Studied populations are heterogeneous, e.g. with regards to disease severity and immunosuppression. Studies assessing viral culture generally include rather small case numbers, especially for time points long after onset of symptoms. One study in South Korea prospectively followed 21 hospitalised patients. The median time from symptom onset to viral clearance in culture was 7 days (95% CI, 5 to 10) and the latest positive viral culture was 12 days after symptom onset (253).

- Studies on dynamics of viral load, contact tracing and modelling studies are consistent in finding that infectiousness peaks around the time of symptom onset.

- The probability of successfully culturing virus seems limited (<5%) 8-10d after symptom onset in mild-moderate cases and 14-20d (or more) in severe cases. A pre-print article does however describe a positive viral culture in a hospitalized patient (no further details) as long as 32d after symptom onset (254).

- Prolonged infectiousness seems to be associated with immunocompromised status, but data is limited. One case report in a patient with lymphoma and impaired B-cell immunity reports a positive viral culture as long as 116 days after first onset of symptoms (255).

- A test-based strategy is hindered by known prolonged shedding of viral RNA, which does not equate with infectiousness. Assessment of viral load might help in these cases but viral loads are usually semi-quantitatively expressed as cycle threshold-values, which differ according to technical lab circumstances and the gene target(s).

Whilst viral culture studies are difficult to interpret and all studies have important methodological limitations, the contact tracing study of Chen et al (Taiwan) is of high quality. In the study, 100 confirmed cases (of which 6 severe) and their 2,761 close contacts are followed up. Only 22 secondary
Asymptomatic infections

Asymptomatic infection at the time of laboratory confirmation has been reported from many settings (227,258–263), including pregnant women (264) and nursing home residents (265). The reported proportions of asymptomatic infections have varied widely, from 17.9% (259) to well over 60% (266). These differences are most likely due to incomplete symptom assessment and lack of follow-up (267) in addition to differences in the underlying study population. One large meta-analysis including 79 studies, concluded that 20% of people [17–25%] remain asymptomatic throughout the course of infection (268). Another review, including only 13 studies at low risk of bias, concluded that 17% of cases remain asymptomatic (14–20%) (269). The last study also suggested that people with asymptomatic infections are less likely to transmit the disease, a finding that is shared by Koh et al in yet another review and meta-analysis of 43 contact tracing studies (270) as well as in various other studies (269,271,272). Seroprevalence studies have sometimes shown much higher proportions of asymptomatic infections, but these results need to be interpreted with caution, as antibody-tests can have problems with specificity (267,273). Interestingly, an article in Nature Communications describes how all 3 children of two infected parents developed an antibody response against SARS-CoV-2, although nasopharyngeal PCR swabs were repeatedly negative (274). Overall, major uncertainties remain with regard to the influence of asymptomatic infections on the overall transmission dynamics of the pandemic. Similar viral loads in symptomatic vs. asymptomatic cases have previously been reported in several other studies (227,234).

Symptoms

COVID-19 can present with a broad spectrum of 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 (226). Other symptoms included fatigue (23%), myalgia (15%), and gastrointestinal symptoms (+8%) (275). Shortness of breath often developed around day 7 after symptom onset. A review in September 2020 of 75 original articles (including 12 RCTs) and 33 systematic reviews or meta-analyses summarized that the most common symptoms were fever (78.0–91.3%), cough (52.0–72.2%), myalgia or fatigue (16.7–51.0%), dyspnea (10.4–45.6%), expectoration (21.3–41.8%) and chest distress (31.2%). Gastrointestinal symptoms occurred in 9.8–17.6%, with diarrhea (7.8–10.4%), nausea or vomiting (5.5–7.7%), abdominal discomfort/pain (3.0–6.9%) and loss of appetite (11%) being the most common symptoms. Fever, dyspnea and gastrointestinal symptoms were more common in severely-ill patients than in mildly-ill patients (276).

As with other systemic viral infections, a large spectrum of possible clinical manifestations have been 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 urticarialia) (277–280). Chemosensory dysfunction, such as anosmia and dysgeusia (either isolated or in combination with other symptoms) are common.
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 (281,282). Notably, anosmia has been reported after infection with other respiratory or coronaviruses (283). Olfactory and/or gustatory dysfunctions are significantly more present in COVID-19 patients compared to patients with acute respiratory infection without detectable virus (OR=11.26) and patients with other respiratory viruses (OR=6.46) (284).

Data from more than 72,000 cases from China classified cases as mild (81%), severe (14%), or critical (5%) (285). 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).

The broad spectrum of atypical COVID-19 symptoms complicates the differential diagnosis with other respiratory infections. The best predictor of a COVID-19 infection are the olfactory and/or gustatory dysfunctions (286). Other symptoms that appear more frequent in COVID-19 in comparison to other respiratory infections are fever, myalgia and general malaise/fatigue (287–290). None of these symptoms was however specific enough to be used in a presumptive differential diagnosis.

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.) (291,292).

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 (293), only few case reports are found in the scientific literature (294,295) 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 (296,297) and a high rate of cardiovascular complications (280). 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) (298). In a double-center study in the Netherlands, a 31% incidence of thrombotic complications in ICU patients with COVID-19 infections is reported (299).

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% (131). In Wuhan, in admitted patients, mortality reached 25% in the middle of the epidemic (275). On March 22, the CFR in the oldest age group (>80y) in Italy was 23% (300). 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% (301). A review of the case-fatality rate in the US found a hospital mortality rate of 15% to 20%, and up to 40% among ICU patients (302). The estimated overall death rate was 46.6 per 1000 confirmed cases, ranging from 0.4/1000 in the age group <18 years old to 304.9/1000 in the age group >=85 years old. The most reliable information to date might come from Spain, where data from excess mortality and a very elaborate population-wide seroprevalence study were used to calculate infection fatality rates. (303) The overall infection fatality
**Long COVID**

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Post-COVID conditions are defined as persistent or new onset symptoms or delayed or long-term complications beyond 4 weeks from the onset of symptoms (304,305). Different terms are used in the literature to describe these conditions, such as long COVID, long-haulers, post-COVID syndrome or chronic COVID syndrome. A comprehensive overview of the available evidence can be found in a policy brief made by the WHO Regional Office for Europe (306).

The pathophysiology is not yet fully understood and consists probably of multiple, intertwined mechanisms (307,308). Two categories of mechanisms are distinguished (306,308): (i) direct organ damage or endothelial dysfunction caused by the virus and (ii) persisting inflammation, thrombosis and autoimmunity.

About a quarter of people who have had COVID-19 exhibit symptoms for a period of 5 weeks or longer and in around 2 to 10% of patients the symptoms persist for a period of 12 weeks or longer (306,308–310). Post-COVID conditions not only appear in patients that have been severely ill but even in patients that remained asymptomatic (305). Havervall and colleagues describe that 10 percent of people who contracted a mild infection without hospitalization are still struggling with at least one symptom of the disease eight months later (311). The COVID Symptoms Study from King’s College London found that long COVID was more likely with increasing age and body mass index and in females (310,312). The researchers also conclude that the more different symptoms people experienced in the first week of their infection, the more likely they are to have persistent symptoms. Case reports on children provide evidence that they can have prolonged symptoms, but these seem less frequent and less severe than in adults (313). In a cross-sectional study conducted by Buonsenso and colleagues, more than half of the 129 included children with laboratory confirmed COVID-19, still suffered from at least one syndrome after four months (314).

Many different organs are affected, in particular heart, lungs and brain (306). The reported long-term complaints are very diverse and overlapping and include amongst others: fatigue, headache, breathing difficulty, loss of smell and taste, generalized chest and muscle pain, muscle weakness, needle pains in arms and legs etc. (306,308,312,315,316). Typically, symptoms fluctuate over time. The multi-organ effects include new-onset diabetes, impaired lung function, pulmonary fibrosis, kidney and liver disease and cardiovascular effects such as ongoing myocardial inflammation or heart failure (317–322). Also, neuropsychological sequelae are suggested such as depression, anxiety, and trauma-related symptoms, psychotic disorders (schizophrenia, psychosis), demyelinating and neuromuscular complications (multiple sclerosis), and neurodegenerative processes (Alzheimer’s disease) (323–326). Taquet et al compared studied patients with COVID-19 during six months after their diagnosis and found neurologic and psychiatric disorders in 1 in 3 patients (327). Risks were greatest in patients who had severe COVID-19 and more common in patients who had COVID-19 than in patients who had influenza or patients who had other respiratory tract infections. A differentiation has to be made between long COVID and the Post-Intensive-Care Syndrome that can occur in any patient after a stay on Intensive Care unit (307,308).

There is no simple test for diagnosing long COVID (306). The NICE guideline lists recommendations for the assessment and investigation of patients with new or ongoing symptoms 4 weeks after acute COVID-19, including blood tests, exercise tests and a thorax X-ray in certain indications (328). Further studies are necessary to know how to follow-up COVID-19 patients but also to prevent these long-term consequences (329). A multidisciplinary, multispecialty approach will most probably be required (306,330). In December 2020, the Belgian Health Care Knowledge Centre (KCE) launched a...
study on the needs and follow-up of people with long COVID. Preliminary results can be found on the website of the KCE and final results are expected by October 2021.

### Immunopathogenesis

**Pathogenesis**

- **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 (331). 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 (331).

Persistence of **high viral loads** has been associated with disease severity (332). 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 (333). 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 (334). In addition, in a study by Huang et al, multiple cytokines and chemokines were found at higher concentrations in hospitalized COVID-19 patients than in healthy adults, among which IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNFα were significantly higher in intensive care unit (ICU) patients than non-ICU patients (335). 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 (336). 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) (334).

Post-mortem autopsies of 3 patients have revealed the presence of viral elements within endothelial cells and a 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 (337).

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 (275,291,338,339). 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 (275). 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 (339). 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.
FACT SHEET
COVID-19 disease (SARS-CoV-2 virus)

15 July 2021, VERSION 11

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In addition, the activation of complement pathways may play a role in severe disease. In one 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 (340).

An additional mechanism of disease pathogenesis hypothesized by several authors is antibody-dependent enhancement (ADE) (341,342). 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 (343). Whether ADE is involved or not in SARS-CoV-2 disease pathogenesis is still unknown.

| 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 a section on ‘Serology’ below. |

Notably, the level of the antibody response mounted after infection shows a positive correlation with the degree of disease severity (344–347). 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 (345,346). 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 (347). 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) (344).

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 (348,349). 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 (350). 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 (351). In this study and others, the magnitude of the nAb response, as for total antibody levels, correlated with disease severity (344,351). 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 >60 days (344).

**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 (352,353). 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 (354). 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 (355).

**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 (356). 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. Various studies have shown that virus-specific T cell responses can be detected in convalescent COVID-19 patients (357–366), even in seronegative patients indicating that immunity can be maintained even in absence of circulating antibodies (357,361,362,367). Higher response frequencies were seen in cases with severe compared with mild disease (357,358,360).

Looking at the T-cell subsets, CD4+ responses were established in 100% of convalescent patients and CD8+ responses in 70% of the cases (364). In the study of Peng et al. (358), it seems that a higher proportion of CD8+ T cell responses was observed in cases with mild disease compared to severe disease. How long these T cell responses remain is too early to know, but it is suggested that they can be detected for a longer period of time (362,363,368,369). For example, memory T cells still existed 6-7 months after infection (368). Further investigation of the phenotype of SARS-CoV-2-specific T-cells was performed in some studies (357,369,370). Virus-specific T cells contain markers indicative for proliferation ability (CD127, Ki-67), CD4+ cells have a Th1 differentiation state and are central memory T cells and T follicular helper cells (critical for antibody production by B cells), and CD8+ cells are predominantly less-differentiated Temra cells.

Using different SARS-CoV-2 epitopes, it was shown that the strongest T-cells responses were against the spike protein (363,364), but also responses against membrane, nucleocapsid, env and ORFs were observed (357–359,362–364). Although not observed in all studies (358,371), it is interesting that in several studies T cell reactivity to SARS-CoV-2 epitopes was detected in 20-60% of healthy individuals (357,359,363–365), which is indicative of the presence of cross-reactivity due to previous infection with 'common cold' coronaviruses (Mateus et al., Braun et al, Nelde et al.). Whether the presence of cross-reactivity might influence the severity of COVID-19 disease is not clear, as well as it is not known yet whether T-cell immunity might protect from reinfection.


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<td>The possibility of SARS-CoV-2 reinfection was raised early on following observations of re-positivity (i.e. individuals tested positive for SARS-CoV-2 more than once) on respiratory samples. Re-positivity can be due to prolonged viral shedding, which is common during SARS-CoV-2 infections, viral reactivation or re-infection.</td>
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**Prolonged viral shedding:** Several reports showed that prolonged viral shedding occurs after SARS-CoV-2 infections, positive PCR results have been observed for up to 40 and 80 days post-initial symptom onset (372). One study even described a positive PCR result 104 days after the first positive test in an obstetric patient (373). A Chinese study found that among 619 discharged COVID-19 cases,
87 (14%) re-tested as SARS-CoV-2 positive in circumstances of social isolation (374). In this study, time between hospital discharge and the re-positive test ranged between 2 to 19 days. In this time frame, re-positivity was more frequently observed in younger patients and/or patients with mild/moderate symptoms (374–376), but there is no established link between a weaker immunity in these cases and the re-positive test. A later meta-analysis showed that the mean shedding duration was 17 days in the upper respiratory tract (maximum shedding duration 83 days), 14.6 days in the lower respiratory tract (maximum 59 days) and 16.6 days in serum samples (maximum 60 days) (377). In this meta-analysis, a positive association was found between a longer duration of shedding and older age. Several studies also reported longer duration of viral shedding in patients with severe illness (377).

Prolonged viral shedding-associated re-positive cases are thought to be non-contagious. In the meta-analysis described above, none of the analysed reports detected live virus beyond 9 days of illness, despite persistently high viral loads (377) 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 44.9 days). 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 (378).

**Reinfection:** 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 (379). The first infection was a mild symptomatic episode, the second was an asymptomatic infection detected through screening upon return from travel.

Since then several cases of reinfection have been described worldwide (254–258, 255).

For all these cases, reinfection was established on the basis of comparative whole genome sequencing, and the identification of single nucleotide variations (SNV). Currently there is no clear definition of the phylogenetic differences that are required to consider viruses from two separate episodes as ‘different’. Analyses were based on the fact that the virus is expected to mutate by two SNVs per month (382, 385). When the viruses from two episodes are associated to different clades or lineages, the evidence of reinfection is stronger (379, 381, 383).

There is currently no clear association between a possibly weaker initial immune response or waning of the immune response and a reinfection episode. In a study performed by To et al, the humoral response of the reinfectious patient was analysed (386). The patient did mount a neutralizing antibody response during the first episode, but this response was not detected at the onset of the second episode, suggesting waning of the humoral response. Nevertheless, high avidity IgG and high titers of neutralizing antibodies were found some days after reinfection, suggesting a robust response during the second episode that might be due to priming of immunity from the first episode. Another study, from Iran, prospectively followed 829 patients with previously confirmed infection. Reinfection mostly occurred in patients without detectable IgG concentration (25/87), and rarely in patients with detectable IgG concentration (1/742) (387).

A large multi-centric prospective cohort study in the UK among 6,614 health care workers (HCW) who were either antibody positive or had a prior positive PCR/antibody test documented 44 reinfections, corresponding with 3.3 reinfections/100,000 person-days and a cumulative incidence of 6.7/1000 (388). In a control group of 14,173 negative HCW, the incidence and cumulative incidence was 17/100,000 pd and 22.4/1000, respectively, corresponding with an adjusted OR for reinfection of 0.17 (95% CI: 0.13-0.24) and thus an 83% lower odds of infection. Similar conclusions were drawn by another prospective study in the UK among 1265 HCW with positive serology and 11,364 health care workers with negative serology (389). Incidence was 0.13 per 10,000 pd among HCW with positive serology and 1.09 per 10,000 pd among HCW with negative serology (adj HR= 0.11; 95% CI: 0.03-0.44).
The potential of virus transmission from re-infected cases is currently unknown. No transmission was reported from the reinfection cases described above, but contact tracing and follow-up was not described in these studies.

It is still unclear how common reinfection can be. In the above-mentioned studies in the UK, reinfection occurred in 0.67% - 0.16% of cases. In the study in Iran, however, 25 of 829 (3.0%) prospectively followed patients got reinfected within one to three months after their first infection, indicating that reinfection might be more common in certain settings.

### Diagnosis and testing

#### Overview

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

Nevertheless, there is currently no perfect ‘gold standard test’ for the diagnosis of COVID-19 to which diagnostic tools can be compared. Reported sensitivities and specificities should be considered with caution. Moreover, the positive and negative predictive values of the test will depend on the prevalence of the virus and therefore on the stage of the epidemic. In addition, timing of testing with regards to symptom onset is an important factor to consider when comparing the diagnostic tools.

Indeed, viral loads in the upper respiratory tract are highest in the day prior and initial days of symptom onset while Chest CT and serology appear to have increased performances later in disease. Knowing the advantages and limitations of each tool is essential, to use tests and interpret results adequately.

#### Laboratory findings

In a retrospective cohort study including 191 PCR-confirmed adult inpatients (Wuhan, China), 40% had lymphopenia (< 0.8 x 10⁹/L), 67% had elevated Lactate dehydrogenase (LDH > 245 U/L), and 80% had >300 µg/L of serum ferritin on hospital admission (275). A systematic review and meta-analysis conducted in April 2020, observed that the most prevalent laboratory finding were increased C-reactive protein (CRP; 73.6%, 95% CI 65.0–81.3%), followed by decreased albumin (62.9%, 95% CI 28.3–91.2%), increased erythrocyte sedimentation rate (61.2%, 95% CI 41.3–81.0%), decreased eosinophils (58.4%, 95% CI 46.5–69.8%), increased interleukin-6 (53.1%, 95% CI 36.0–70.0%), lymphopenia (47.9%, 95% CI 41.6–54.9%), and increased lactate dehydrogenase (LDH; 46.2%, 95% CI 37.9–54.7%). A meta-analysis of seven studies showed that increased CRP (OR 3.0, 95% CI: 2.1–4.4), lymphopenia (OR 4.5, 95% CI: 3.3–6.0), and increased LDH (OR 6.7, 95% CI: 2.4–18.9) were significantly associated with severity (390).

#### RT-PCR

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

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

- **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 has been obtained.

  **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 (391). 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. Another systematic review of 32 studies came to similar conclusions. The highest percentage virus detection through nasopharyngeal sampling was between 0 and 4 days post-symptom onset at 89% (CI, 83% to 93%) dropping to 54% (CI, 47% to 61%) after 10 to 14 days (392).

With regards to sample type: Sensitivity of RT-PCR appears to be higher for lower respiratory samples than for upper respiratory tract samples (202, 233, 393). In a study including 213 COVID-19 cases and analyzing 866 respiratory tract samples (Shenzhen, China), in the first week of symptom onset, sputum samples showed the highest positive rate in both severe (88.9%) and mild (82.2%) cases, followed by naso-pharyngeal swabs (73.3%, 72.1%) and throat swabs (60.0%, 61.3%). BAL showed 100% sensitivity in severe cases in days 8 to 14 of onset. In this time period, positive rate of sputum remained higher than that of naso-pharyngeal swabs, and positive rates of pharyngeal samples dropped to 50% in severe and 29.6% in mild cases. This is not unexpected as viral load in the upper respiratory tract is highest one day before and the days immediately after onset of symptoms (234–237). RT-PCR may remain positive longer in lower respiratory samples (233, 393). 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 (393).

Sensitivity of RT-PCR on oral fluid samples is discussed further in the document.

- **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 (394, 395), 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%) (396). With the exception of SARS-CoV, no cross-reactivity is found when tested against a large panel of microorganisms including the common human coronaviruses (397). 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.

**Rapid RT-PCR tests.** Most RT-PCR tests take 4 to 6 hours to get the result. However, certain platforms, such as GeneXpert, provide faster results (in about 15–45 minutes), and these are often referred to as ‘rapid PCR tests’. Their performance in terms of sensitivity and specificity is similar to that of the standard RT-PCR tests (398), but their cost is higher.

**Impact on other respiratory viruses and multiplex PCR**

Multiplex PCRs have been used to analyze transmission patterns of different respiratory pathogens as well as to assess the extent of co-infections of SARS-CoV-2 and other common respiratory pathogens, and its impact on clinical outcomes.

A study assessing the impact of SARS-CoV-2 on the prevalence of respiratory viruses in hospitalized patients, found that in March-May 2020 non-SARS-CoV-2 viruses (such as Influenza, rhinovirus, RSV, seasonal coronaviruses or parainfluenza virus) were present in only 4.1 % of the samples, while in the same period in 2019 they were detected in 54% of the patients (399). The emergence of SARS-CoV-2...
was therefore associated with reductions in the circulation of seasonal respiratory viruses. The authors concluded that this observation could be due to the measures taken to fight COVID-19, such as social distancing and lock-down. Another hypothesis points at interactions and interferences between different viruses. This has been shown for other respiratory viruses (400). Reduction in the circulation of other seasonal respiratory viruses during the first peak of the epidemic was also observed in several regions worldwide (401,402). An early Italian study however did not see different trends for other respiratory viruses in March 2020 compared to the same period in previous years (403).

Co-infections of SARS-CoV-2 and other respiratory viruses have been described in several reports, the extent of co-infections is variable. In most studies coinfection was found in only 1% to 2% of the samples (404,405). Some studies observed more extended cases of co-infections with bacterial pathogens (406).

However, COVID-19 patients co-infected with influenza had in one study a 2.27 times greater risk of death than non-co-infected patients (407). Detecting co-infection, using a multiplex PCR, is therefore generally recommended in patients with severe or complicated disease or those with risk factors, when there is evidence of a seasonal epidemic of other respiratory viruses, such as influenza.

<table>
<thead>
<tr>
<th><strong>Other Nucleic Acid Amplification Tests</strong></th>
<th><strong>Tests</strong></th>
<th><strong>Last update</strong></th>
<th>09 April 2021</th>
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<tbody>
<tr>
<td>There are a number of Nucleic Acid Amplification Tests (NAATs) that detect SARS-CoV-2, using a different technique than reverse transcriptase polymerase chain reaction. Most use isothermal amplification methods, such as transcription mediated amplification (TMA), strand displacement amplification (SDA) or loop-mediated isothermal amplification (LAMP), and some use CRISPR-Cas technology (408,409). Their specificity is similar to that of an RT-PCR, but their sensitivity is slightly lower (410).</td>
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<th><strong>Oral fluid samples</strong></th>
<th><strong>Last update</strong></th>
<th>13 July 2021</th>
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<tr>
<td>Oral fluid collection instead of using nasopharyngeal (NPS) or oral/nasal swabs for RT-PCR has been suggested and is now used in certain circumstances. Methods vary widely: from posterior oropharyngeal fluids/saliva collected by spitting or drooling, or collection of oral fluid with pipet or special sponges. Gargling with saline solutions is another alternative that has been studied. Salivary samples can facilitate the sampling procedure, decrease discomfort of sampling, decrease exposure risks and, through self-sampling, decrease the workload of health care workers.</td>
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<td>Sensitivity of these specimens has a wide performance range compared with naso- and/or oropharyngeal sampling. Several systematic reviews and meta-analyses have been published to date (411–418). The pooled sensitivity of RT-PCR on saliva samples is generally around 85% and 2 to 5% lower than the pooled sensitivity of RT-PCR on a nasopharyngeal sample. They conclude that saliva specimens play a role in the detection of SARS-CoV-2. Sensitivity is overall similar in patients with a high viral load (Ct value&lt;=25). Saliva specimens are sometimes effective in detecting infections in people testing negative with a nasopharyngeal sample, possibly because of viral nucleic acids from the duct of the salivary gland.</td>
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| A Belgian study in 107 confirmed cases found a sensitivity of 97% of spitted saliva samples with medium and high viral loads (above 20.000 copies/ml), but <5% in samples with low viral loads (below 20.000 copies/ml) (419). 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. 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) (420). Hung et al. found an overall trend of lower Ct values in posterior oropharyngeal saliva collected in the early morning, with a gradual decrease of viral load towards nighttime (421). 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 (422). Sensitivity also depends on how the saliva is collected. In a study of Chen et al., with posterior oropharyngeal secretions (POPS), no significant difference in detection rates between NPS and saliva samples was found (212). POPS specimens might contain both bronchopulmonary secretions and nasopharyngeal secretions, resulting in a higher sensitivity compared to saliva straight from salivary glands (424). A Belgian study found that gargled samples had a better sensitivity (74.0%) than spitted samples (68.2%) and in patients with certain symptoms, such as rhinorrhea, anosmia or a sore
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 (428).


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 (429). Inversely, negative Chest CT in PCR positive patients has also been reported (430), 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 (431). 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 (432). 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 (263). Similarly, on the “Diamond Princess cruise ship”, 41 out of 76 asymptomatic cases (54%) had abnormal CT findings (433).

All these studies evaluated saliva collected under supervision of a health care provider, few studies assessed unsupervised collection. One study compared both approaches and found that overall sensitivity in self-collected samples was much lower than in saliva specimens collected under supervision (66.7% and 86%, respectively) (426). However, the difference was less in samples with a Ct value <=25 (93.3% and 100%, respectively).

Most studies, however, assessed the performance of saliva specimens among symptomatic people (hospitalized patients or people attending an OPD or an emergency department and only few assessed performance in a context of screening asymptomatic people. An interesting study in Japan assessed, over a 7 days period, the sensitivity of different tests on nasopharyngeal, anterior nasal and saliva samples taken from 20 asymptomatic air travellers (427). On a total of 97 samples tested, the sensitivity compared to RT-PCR on NPS was 64%, comparable to the sensitivity of a rapid Ag test on a NPS (60%). Among 33 samples with viral load ≥ 10⁴ copies/sample, sensitivity was 100% and equal to the sensitivity of the rapid Ag test on NPS.

The consensus is that saliva samples are in particular of use in the context of repeated screening of asymptomatic adults, because of the good acceptability for patient and caregiver (and thus the sensitivity of a testing strategy) and because the reduced sensitivity to the individual test is compensated by the testing frequency (see further below). Saliva is also equivalent to a nasopharyngeal swab when viral load is high, such as in patients with recent onset of symptoms (<5 days).

For the use of oral fluids for rapid antigen testing see further below.

<table>
<thead>
<tr>
<th>Chest CT Last update</th>
<th>19 April 2020</th>
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<tbody>
<tr>
<td>Had abnormal CT findings</td>
<td>Head, neck, and thorax, a higher sensitivity than NPS (Defèche et al. In-depth comparison of clinical specimens to detect SARS-CoV-2). Also in another study gargling had a higher sensitivity than spitting (98% vs. 79%), and a higher acceptability (425).</td>
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| Typical radiological findings | In patients tested between days 3 to 5 (431), 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 (431). 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 (432). 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 (263). Similarly, on the “Diamond Princess cruise ship”, 41 out of 76 asymptomatic cases (54%) had abnormal CT findings (433). |


| Chest CT | 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 (429). Inversely, negative Chest CT in PCR positive patients has also been reported (430), 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 (431). 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 (432). 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 (263). Similarly, on the “Diamond Princess cruise ship”, 41 out of 76 asymptomatic cases (54%) had abnormal CT findings (433). |
**FACT SHEET**  
**COVID-19 disease (SARS-CoV-2 virus)**  
*15 July 2021, VERSION 11*

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<tr>
<th><strong>Chest CT lacks however in specificity.</strong> 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.</th>
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| **Serology**  
**Last update**  
**13 July 2021**  
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) (434) 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 over time while others found antibody persistence for at least 120 days.  
- Correlation between antibody levels and protection against reinfection or disease is currently unknown (347,435)  
Data on seroconversion in asymptomatic and pauci-symptomatic cases is emerging. 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 (436).  
**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) (437). 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 %)(438). An evaluation of COVID 19 serological assays found sensitivities ranging from 81 to 99 % and specificities ranging from 94 to 99 % (437).  
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 a lower respiratory tract infections) (439). Inversely, cross-reactivity has been found when sera from SARS-CoV-2 patients are tested using SARS-CoV serological assays (440). 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, or for distinguishing between old and new infections when viral load is low. Indications for which a serology test is reimbursed in Belgium can be found here.

IDSA (441) published recommendations in which potential indications for serological 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 (442).

<table>
<thead>
<tr>
<th>Rapid Ag and Ab tests</th>
<th>Last update 14 June 2020</th>
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<tr>
<td>Rapid tests have been developed with the idea of a point-of-care approach, offering rapid results (within 10-30 minutes). Rapid tests have been developed both for the detection of antigens and for the detection of antibodies.</td>
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<td>Rapid antigen tests: These tests are immune-chromatographic assays, and involve the detection of SARS-CoV-2 antigen in respiratory samples. An initial test validated in Belgium in April 2020 showed a high specificity (100%), but low sensitivity (56-60%), compared to the RT-PCR (443). Some later developed tests show, however, better performance with overall sensitivities of around 80% (444,445). Sensitivity is generally much better when viral load (Ct&lt;25) is high, such as in patients with recent symptoms. Some argue therefore that the lower sensitivity is not necessarily problematic, because it might be mainly less infectious patients that are missed (446). Performance varies substantially between tests and between studies, and some rapid Ag tests available on the Belgian market perform rather badly (447). A Cochrane review of studies assessing four different rapid Ag tests found an average sensitivity of 56.2% and specificity of 99.5%, but the authors pointed out that care had to be taken with interpreting the average because the very large difference between tests and studies (448).</td>
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<td>The use of rapid antigen tests is therefore mainly considered in patients with recent onset of symptoms (&lt;=5 days), when viral load is still high, and for screenings where a rapid result is needed, for example to rapidly isolate positive cases in outbreaks, for screening people who will come in contact with vulnerable populations (such as visitors to nursing homes) or pre-event screening of participants of a mass-event. Rapid Ag tests can also be used for repetitive testing, where the lower sensitivity is compensated by the testing frequency.</td>
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<td>Automated antigen tests: These tests detect SARS-CoV-2 antigen, using techniques such as chemiluminescence, on automated machines, thereby allowing high-throughput of samples. They can process samples in less than one hour per run, and are less expensive and laborious than RT-PCR testing. Their performance is similar to that of rapid antigen tests.</td>
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**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% (449). A 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%) (450). 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 (450). 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.

**Repetitive testing**  
*Last update 5 February 2021*

Repetitive or repeat testing in specific populations has been proposed as a strategy to early detect asymptomatic cases and thereby prevent outbreaks. Several modelling studies have demonstrated that frequent testing with a less sensitive test (rapid antigen test) or a less sensitive sample (saliva) is more effective than one-time testing with the more sensitive RT-PCR on a naso-pharyngeal sample (451–453). Most studies recommend a periodicity of at least 2–3 times a week (454–457), but others state that relatively infrequent testing, such as every one or two weeks, is already sufficient to keep controlled outbreaks small (458). One study modelled the potential impact of different testing and isolation strategies on SARS-CoV-2 transmission, defined as the percentage reduction in R. Self-isolation of symptomatic individuals would result in a reduction in R of 47%, and weekly screening of health-care workers and other high-risk groups irrespective of symptoms by use of PCR testing by an additional 23%, assuming results are available at 24 h (459). Models also show that the health benefits of repeated testing with a rapid antigen test far exceed their costs (460).

Studies evaluating the effect of repetitive screening in a real-life situation are, however, rare. In addition, the few available publications often focus on acceptability only. Little is, for example, known about the possible effect on behavior change as a result of knowing the test result. The current Belgian recommendations recommend it therefor only for people who come in frequent contact with people vulnerable to severe disease, such as staff in nursing homes. In certain other situations, it is considered as potentially useful but not a priority.

Studies assessing the effect of regular universal testing overall conclude that it might help to reduce infections but that it would require unrealistic high testing frequencies (461,462). A modelling exercise by UHasselt showed, on the other hand, that weekly universal testing, by pooling samples of individuals that belong to the same households, is able to control the epidemic, even when many of the contact reductions are relieved (463).

**Testing sewage water**  
*Last update 3 February 2021*

An interesting method to early detect SARS-CoV-2 presence is through regular monitoring of sewage water. SARS-CoV-2 has been found in the faeces of infected patients in numerous studies. Although no evidence of COVID-19 transmission has been found via this route, monitoring of SARS-CoV-2 in sewage could be advantageously exploited as an early warning of outbreaks (464,465).

**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 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).

**For international epidemiological updates:**
- John Hopkins Coronavirus Resource Center: [https://coronavirus.jhu.edu/map.html](https://coronavirus.jhu.edu/map.html)
- Our World in Data: [Coronavirus Pandemic (COVID-19) - Statistics and Research - Our World in Data](https://ourworldindata.org/coronavirus)

<table>
<thead>
<tr>
<th>Basic reproductive number</th>
<th>The basic reproductive number, the so-called R₀, of the virus is thought to be between 2-4 (466) 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 (Rₑ) 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) (467). In the United Kingdom, &quot;lockdown&quot; 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 prior to lockdown to 0.62 (95% CI 0.37 -0.89) after the lockdown (468). 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 (469).</th>
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<td>Last update</td>
<td>14 June 2020</td>
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| Effect of climate | Impact of meteorological conditions on the transmission dynamics of SARS-CoV-2 is still debated. 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 behaviours 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 (470–472). Concerning SARS-CoV-2, available data is not always conclusive. Studies evaluating effect of climate on outbreak dynamics across several countries have not always taken into consideration country differences with regards to containment measures or disease-reporting system (473,474). Moreover, certain studies have considered meteorological parameters only, without correcting for other parameters impacting disease dynamics, such as population density, population age distribution, etc (475). 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 (476). Inversely, a spatio-temporal analysis exploring the effect of daily temperature on the accumulated |
| Last update | 14 July 2021 |
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 travellers were considered in the analysis (477).

A systematic review of 11 studies and meta-analysis on correlation of weather with COVID-19 found significant correlation between incidence and temperature (0.22 [95% CI, 0.16–0.28]), humidity (0.14 [95% CI 0.07–0.20]) and wind speed (0.58 [95% CI 0.49–0.66]) (478). The authors concluded that weather can be considered as an important element regarding COVID-19 spread. Another more extensive review concluded that it remains unclear to what extent the effect of temperature or humidity on COVID-19 is confounded by the public health measures implemented (479). The effect of weather and climate variables cannot be excluded, however, the increase in the number of cases observed during summertime in the Northern hemisphere, and especially in countries with high average ambient temperatures, demonstrates that weather and climate variables, in the absence of public health interventions, cannot mitigate the resurgence of COVID-19 outbreaks.

On the other hand, differences in climate might be a contributing factor for differences in incidence between countries. A study analyzing the effect of heat and humidity on the incidence and mortality in the world's top ten hottest and top ten coldest countries, found a significant decrease in incidence and deaths in countries with high temperatures and low humidity, compared to countries with low temperatures and high humidity (480).

### Special populations

| Risk groups & Risk factors | The most important risk factors for severe disease and poor outcome are older age and the presence of comorbidities, in particular hypertension, cardiovascular diseases (CVD), diabetes mellitus, chronic obstructive pulmonary disease (COPD), malignancy, and chronic kidney disease. Other factors that have shown to increase the risk of a poor outcome are male gender, smoking and obesity. Populations with a higher risk comprise pregnant women, HIV patients and people with Down Syndrome. A systematic review of 114 articles assessing predictors of mortality in patients with COVID-19 found that older age, hypertension, and diabetes mellitus were most commonly associated with a significant increased risk of mortality, although that in the multivariate analysis, only diabetes mellitus demonstrated an independent relationship with increased mortality (481).

**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%) (285). 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) (275). Liu et al have reported on another retrospective cohort study of hospitalized patients in Wuhan. Among 109 COVID-19 confirmed patients, 53 (48.6%) of them developed Acute Respiratory Distress Syndrome (ARDS). Compared with non-ARDS patients, in univariate analysis, patients with ARDS were older (mean age, 61 years vs. 49 years; p<0.001), and more likely to have underlying co-morbidities (482). A review of the case-fatality rate in the US found that the estimated overall death rate ranged from 0.4/1000 in the age group <18 years old to 304.9/1000 in the age group >=85 years old (302). Older age was also one of the best predictors of in-hospital mortality in the multivariate analysis of risk factors for mortality in 319 hospitalized patients in Belgium (483).

**Co-morbidities**: In a meta-analysis (10 articles, 76993 patients overall), the most prevalent underlying diseases found among hospitalized COVID-19 patients were hypertension, cardiovascular diseases (CVD), diabetes mellitus, smoking, chronic obstructive pulmonary disease (COPD), malignancy, and chronic kidney disease (484). A later systematic review of 27 articles consisting of 22,753 patient cases worldwide found similar results: hypertension was the most common...
comorbidity (27.4%), followed by diabetes (17.4%) and cardiovascular diseases (8.9%). Other comorbidities included COPD (7.5%), cancer (3.5%) and chronic kidney disease (2.6%) (485). 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) (482). 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 (275).

A meta-meta-analysis of the effect of cardiovascular comorbidities on the severity of COVID-19 found that the odds of getting severe COVID-19 is more than 3 times higher in patients with CVD (OR=3.44), and more than 2.5 times higher in patients with hypertension (OR=2.68) (486).

Although less common, some studies documented an association between neurologic disorders and severe COVID-19 (487–490).

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 (285). In the Lombardy (Italy) outbreak, a large retrospective case-series on 1591 COVID-19 patients admitted to ICU, 82% were male (301). 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 (275). 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 (482). Several other studies found a higher risk of severe outcome and/or death among male compared to female COVID-19 patients, after adjusting for other risk factors (488,491–493). A meta-analysis of 20 studies (the majority from China) found a significant increased risk of mortality in males compared to females (RR=1.86; 95% CI 1.67-2.07) (494). A possible explanation for the increased risk is a sex-based difference in the expression of the ACE2 receptor and transmembrane protease serine 2 (TMPRSS2) that enhances a successful entry of SARS-CoV-2 into the body (495,496).

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 (275). 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 (497).

A systematic review and meta-analysis of 16 articles (11,322 patients) established an increased odds for severe COVID-19 disease in patients with a history of smoking (OR=2.17; 95% CI: 1.37–3.46) and in patients currently smoking (OR=1.51; 95% CI: 1.12–2.05). In 10.7% (978/9067) of non-smokers, COVID-19 was severe, while in active smokers, severe COVID-19 occurred in 21.2% (65/305) of cases (498).

Obesity: Obesity has emerged as an independent risk factor for susceptibility to and severity of COVID-19 (491,499). In a meta-analysis of 14 studies, patients with a BMI > 25 kg/m2 had a more than 3.5 greater odds to have died (OR=3.68; p=0.005) (500).
**Ethnicity:** Role of ethnicity has been studied and reported in COVID-19 surveillance. Ethnicity is, however, a complex entity composed of genetic make-up, social constructs, cultural identity, and behavioural patterns, that all may influence COVID-19 disease.

A review and meta-analysis of 59 cohort studies and 13 ecological studies from the US and the UK could not confirm a certain ethnicity as an independent poor prognostic factor for COVID-19. Age- and sex-adjusted risks were significantly elevated for Black (HR: 1.38 [1.09–1.75]) and Asian (HR: 1.42 [1.15–1.75]), but not for Hispanic (HR:1.14 [0.93–1.40]). Further adjusting for comorbidities attenuated these associations to non-significance: Black (HR: 0.95 [0.72–1.25]); Asian (HR: 1.17 [0.84–1.63]); Hispanic (HR: 0.94 [0.63–1.44]) (501). On the other hand, another review of 35 papers, also of the US and the UK, found that after adjusting for confounders, individuals of Black ethnicity (adj. RR: 2.06, 95% CI: 1.59–2.67), Asian ethnicity (adj. RR: 1.35, 95% CI: 1.15–1.59) and Hispanic ethnicity (adj. RR: 1.77, 95% CI: 1.39–2.25) had all a higher risk of SARS-CoV-2 compared to those of White ethnicity (502). Individuals of Black and Hispanic ethnicity were also more likely to be admitted to ICU.

**Health-care workers:** cfr section on health-care workers in ECDC document ‘Disease background of COVID-19’.

**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) (503). 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 (504,505). 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 (506). 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 | 14 December 2020 |

Children are less affected by COVID-19 than adults and are more likely to have mild or asymptomatic infection (507). Between 1st of August and 29th of November 2020, cases in children <12y made up 5.2% of total individual reported cases in the EU, whereas this age group makes up 10.6% of the total population. Confirmed cases are more frequent in children 12-18y (7.4% of all confirmed cases, age group represents 6.8% of the total population) but very few cases require hospitalization: 1.54% of all total hospitalizations are in this age group. (ECDC dashboard). In Belgium, most of the hospitalized children (81%) had no severe event. Only a proportion of 3% was admitted to ICU (report Sciensano – situation until end of June). Fatal outcome in children is extremely rare.

**Even after a known exposure, children seem less likely to become infected.**

In countries where widespread community testing (either PCR or serology) has been implemented, children were less likely to test positive than adults (508–512). However, these results might be biased if children had less exposure to the virus, e.g. because school closures were in place. Yet, even after a known exposure within the household, data from contact tracing studies indicate that children are less likely to get infected than adults (513–517). Mathematical modelling concluded that children are about half as likely to get infected as adults (513), a conclusion that was supported by a meta-analysis of contact tracing data by Viner et al (517). Another later meta-analysis by Koh et al. pooled data from 14 contact tracing studies and, likewise, found adults more likely to become...
infected after exposure within the household than children (<18y), with a RR of 1.71 [1.35-2.17], although there was considerable heterogeneity among the included studies. These effects seem greater for younger children (either <5y or <10y) compared to older children (518). Several mechanisms have been proposed to explain this relative resistance, from immune imprinting by other viruses (519) to distribution, maturation, and functioning of viral receptors (520). Seroprevalence data have sometimes shown higher-than-expected antibody-detection rates but need to be interpreted with caution: see “asymptomatic infections”.

The role of children in the transmission dynamics of SARS-CoV-2 remains much debated (521) although there exists a consensus that young children are not the drivers of transmission (522). 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 (523). 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 not significantly different from those of adults (524). However, transmission dynamics are not only determined by the biological component, but also by behavioral and contextual components. Most children appear to be infected within their households (525). 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) (526,527) and children rarely cause secondary cases (528,529). A ‘lower risk of onwards transmission’ is however not zero risk: transmission has been described from daycare settings in Poland (530) and the US (531). Reassuringly though, a large study from the US looked at the risk of COVID-19 infection and being a child care provider (for children <6y old). Data was gathered on a total of 57,335 child care providers, of which 427 were reported COVID-19 cases. After correcting for background transmission rates and other demographic variables and potential confounders, no association was found between exposure to child care and COVID-19 infection (532).

Data on transmission in school settings is increasing. Contact tracing and cluster investigations in schools before lockdown done in Ireland (533), France (534,535) and New South Wales (536) 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 (537). Data from Public Health England showed outbreaks were rare and mostly linked to staff or older students. The risk of having an outbreak in a school correlated with the level of community transmission (538). Cluster investigations in Germany (539) and Italy (540) confirm these findings. Likewise, seroprevalence studies have demonstrated that the infection attack rate in high school students (38.3%) was higher than in primary school students (8.8%) (534,535) and a large outbreak in a high school in Israel, with an infection in 153 students and 25 staff members (541), received a lot of attention.

In conclusion: children, especially in primary school, do not seem to be the drivers of the epidemic. Onwards transmission is however possible and children should be kept home when they are sick or when there is a COVID-infection in the household. It is important that mitigation measures are in place in schools. Adolescents (16-18y) seem to spread the virus in the same way as adults.

Additional information and recent numbers for Belgium can be found in the RAG advice on transmission in primary schools.

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 MIS-C Multisystem Inflammatory syndrome in children (previously also PIMS-TS, Pediatric Inflammatory Multisystem Syndrome Temporally-associated with SARS-CoV-2). Initial case definitions have been released by the Royal College of Paediatrics and Child Health, the CDC, and the World Health Organization (542). The syndrome is rare and an increase in cases seems to occur weeks after the COVID-19 epidemic peak, apparently in places that are heavily affected (543). Several case series of PIMS-TS have been reported and describe a wide spectrum of presenting signs and symptoms and disease severity, ranging from fever and inflammation to myocardial injury.
### 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 (549). However, preliminary data from small case series, reported similar clinical characteristics in pregnant women as in the general population (550–555). These findings were then confirmed in obstetric surveillance data from the UK (556) and a prospective cohort from NYC (557). 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 (558). 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 (559). 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. An update of the CDC report was published November 6th. The report includes data on 409,462 women of reproductive age with COVID-19 (symptoms and positive test) of which 23,434 were pregnant (560). This time, not only an increased risk was found for ICU admission of pregnant women vs. non-pregnant women (aRR 3.0 [2.6–3.4]) but also for mortality (aRR 1.7 [1.2–2.4]). However, the main limitations of the data still exist: information on pregnancy status is missing for 64.4% of women in reproductive age and there is no information on reason for hospital/ICU admission (i.e. COVID-related vs. pregnancy related). A smaller observational cohort, also from the US, including 3,374 pregnant women of which 252 SARS-CoV+, reported that only 5% of women were hospitalized for COVID-19 reasons, which was similar to the reported hospitalization rate of non-pregnant women in the CDC report (561). Finally, an analysis of administrative data from the US (using ICD-10 codes and reimbursement codes) compared outcomes in 400,066 pregnant women without COVID-19 with 6,380 women with COVID-19. Although absolute risks were low, an increased risk was noted for thrombotic events, ICU admission and mechanical ventilation in the women with COVID-19. Of note is that the comorbidities were frequent in the included population, with 17% of the pregnant COVID+ women being obese and 5% even having a BMI >40 (562).

In conclusion, pregnant women with SARS-CoV-2 seem to be at relatively higher risk of ICU admission, although absolute risks are low. As with non-pregnant women, risk factors like pre-existing comorbidities and age play a role. Based on experience with other respiratory infections and physiological changes, the highest risk would be expected in the third trimester. Of note is that, like the non-pregnant population, many pregnant women will have a mild or even completely asymptomatic course of the disease, as was shown again by e.g. a seroprevalence study from Madrid (563).

### Risk to the fetus

In utero transmission is possible, as proven by a case from France (564). 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
FACT SHEET
COVID-19 disease (SARS-CoV-2 virus)

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<tr>
<th>Other special populations</th>
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<tr>
<td>HIV patients: The few available case-reports of SARS-CoV or MERS-CoV infection in patients with AIDS described mild disease symptoms and recovery (573,574). 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 (575–580). Similar conclusions are drawn from later matched case-control studies comparing HIV and non-HIV patients, albeit limited in size (581,582). 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 77,590 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 (583). A large cohort study in New York, prospectively following 2988 PLWH with COVID-19 found that COVID-19 cases living with HIV were more often hospitalized (sRR=1.47; 95%CI 1.37-1.56) than COVID-19 cases without HIV (584). A rapid meta-analysis of 19 studies found that in five studies PLWH had a higher risk of COVID-19 mortality (HR=1.93, 95%CI: 1.59-2.34) and eight studies provide inconclusive, lower quality evidence (585). The authors concluded that evidence is emerging that suggests a moderately increased risk of COVID-19 mortality amongst PLWH, and that further investigation is warranted. 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 (586).</td>
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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 (564–567). 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 (565). 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 (568,569). Pre-term and cesarean delivery rates seem related to geographical differences rather than being a result of COVID-19 (570). Some authors have warned for the possibility of intrauterine growth restriction (551), a concern that is strengthened by the findings of increased vasculopathy in placentas from mothers with SARS-CoV-2 (566,571).

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 (567,572).
| Overall, as expressed in the 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 (587).

Importantly, although mild presentation and recovery from COVID-19 severe disease has been described in severely immunocompromised PLHIV (576,579), 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”.

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 (588,589).

| 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 (590–593). Most frequent cancer types reported among COVID-19 hospitalized patients are lung, breast, gastrointestinal, genitourinary, prostate and hematological (594–599). Case-fatality rate (CFR) in cancer patients with COVID-19 ranges between 11% to 32% (594–600). 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%) (596,600). Among solid cancer patients, patients with lung cancer have been shown to have the highest death rate and highest frequency of severe events (599). 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%) (601). 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 (592,598).

Two larger studies on COVID-19 in patients with hematological malignancies have been conducted (602,603). 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 (602). 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 (597–600,604). On the other hand, Yang et al. describes chemotherapy as a risk factor for in-hospital death (596). Receiving radiotherapy was also suggested to be associated with increased mortality (605). The study from Dai et al. suggests that patients with surgery or immunotherapy have a higher death rate (599). 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


**People with Down Syndrome:** Case reports of people with Down Syndrome (DS) who had a more severe COVID-19 disease course raised concerns that this population might be more at risk (606,607). A study in Iran consecutively following 37,968 hospitalized patients of which 18 had DS, found that they were significantly more likely to be intubated and significantly more often died of COVID-19 compared to the controls [8 (44.4%) vs. (1.9%); OR: 24.37; 95% CI 2.39–247.94] (608). A larger international survey documented disease course and outcome of 1046 COVID-19 patients with DS (609). Disease outcome in 100 DS patients was compared with the outcome in 400 matched controls. Risk factors for hospitalization and mortality were similar to the general population (age, male gender, diabetes, obesity, dementia) with the addition of congenital heart defects as a risk factor for hospitalization. Mortality rates showed a rapid increase from age 40 and were higher than for controls (RR=3.5 (95%CI=2.6;6.4) versus RR=2.9 (95%CI=2.1;3.8)) even after adjusting for known COVID-19 mortality risk factors. A possible factor explaining this higher risk is immune-response dysfunctions that are common in people with DS (610).

### Patient management

**Treatment**

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Symptomatic and optimal supportive care is the mainstay of treatment for COVID-19. In addition to standard care (e.g. antipyretics, fluid management, treatment of co-infections or superinfection) etc., specifics are required with regards to **preventive anticoagulation** (see recommendations BSTH) and **oxygenation** (see recommendations: hospital-setting **FR/NL**, ambulatory **FR/NL**). Self-medication & the interruption of chronic treatments without medical advice is strongly discouraged.

**Multiple treatment strategies, including re-purposing of older drugs, are under investigation.** An interim guidance for the treatment of hospitalized cases in Belgium is available ([link](https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic)) and includes a review of literature and a summary of the ongoing clinical trials in Belgium. Drugs covered in the document are corticosteroids, remdesivir, hydroxychloroquine, lopinavir/ritonavir, remdesivir, favipiravir, camostat mesylate, immunomodulatory agents (eg. anti-IL6, anti-IL-1), convalescent plasma, interferons, monoclonal antibodies, baricitinib, azithromycin, interferons, ivermectin, colchicine and aspirin.


Many questions have arisen with regards to the use of **Non-steroid anti-inflammatory drugs (NSAIDs)** and Angiotensin-converting enzyme inhibitors (ACEI)/Angiotensin receptor blockers (ARBs). There is currently no evidence from clinical or epidemiological studies that establishes a link between their use and severe COVID 19 (611,612). An RCT found no impact of ACEI/ARB switch in COVID-19 (613). The same type of concerns were raised for non-steroidal anti-inflammatory drugs (NSAIDs), with also no evidence so far to advise for or against these drugs in COVID-19 patients. A nationwide cohort study in Denmark found no difference in COVID-19 outcome in patients with recent use of NSAID (614). However, to be safe, and while waiting 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 (as in common practice) and according to common practice (contra-indicated in case of renal failure for example).

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