

FACT SHEET

COVID-19 disease (SARS-CoV-2 virus)

08 June 2022, VERSION 16

Disclaimer :

The basic characteristics of SARS-CoV-2 are now known and the speed of research is slowing down. Therefore, the fact sheet will not be further updated.

This document has been written by scientists from the Epidemiology of Infectious Diseases Unit of Sciensano. Contributing authors are (in alphabetical order): Laura Cornelisssen, Géraldine De Muylder, Yves Lafort, Valeska Laisnez, Amber Litzroth, Giulietta Stefani, Veerle Stouten, Els Van Valkenborgh, Chloé Wyndham Thomas

Over **250,000** 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which discoveries are being made, certain references included are preprint papers or rapid communications that have not yet been peer-reviewed. Critical appraisal of the content is, as always in our discipline, encouraged.

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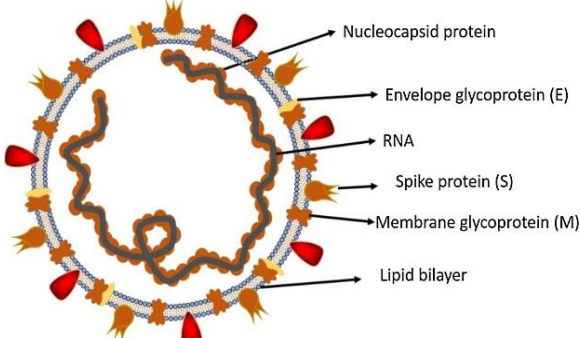
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Note: Highlighted sections in this document are those that have been added or updated since version 15 (22 March 2022)

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Pathogen	
<p>Virology Last update 4 September 2020</p>	<p>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).</p> <p>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).</p> <p>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.</p> <div style="text-align: center;">  </div> <p style="text-align: center;"><i>Figure 1. Structure of respiratory syndrome causing human coronavirus (2)</i></p> <p>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).</p> <p>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).</p>
<p>Genetic diversity & viral variants Last update 22 March 2022</p>	<p>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</p>

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	<p>weak. Updates on the distribution of variants in Belgium is available on the NRC website, in Europe on the ECDC website and in the world on the WHO website.</p> <p>D614G variant. Till beginning 2021, the main circulating variant of SARS-CoV-2 was the D614G variant (also referred to as G614), resulting from an 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).</p>
	<p>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 later referred to as the Alpha variant), was identified in the United Kingdom (6,7). The variant was defined by 14 mutations resulting in amino acid changes and three deletions, some of which influence the virus's transmissibility in humans. The rate of transmission of the variant was higher than for other variants (8–12). A rapid scoping review in pre-print found reported increases of risk of transmission ranging from 45% to 71% (13).</p> <p>A study coordinated by the ECDC compared the hospitalisation rate of the Alpha variant to the rate among non-VOC 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) (14). 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.</p> <p>The Alpha variant rapidly became the predominant variant in Europe and worldwide (15). 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 (16). However, since then its share declined due to the rise of the Delta variant (see below) and after August 2021 it was detected in less than 1% of all baseline surveillance samples.</p> <p>An additional mutation (E484K - a mutation improving the ability of the virus to evade the host's immune system) occurred in the Alpha variant and it was expected that this could lead to a reduced sensitivity to immunity induced by previous variants (17). The spread of this subtype (named B.1.1.7 with E484K) remained, however, limited.</p>
	<p>Beta variant. One of the mutations identified in the Alpha variant (N501Y) had also been reported in South Africa, where it arose independently of the Alpha variant (18). The variant, named 501Y.V2, lineage B.1.351, initially referred to as the 'South Africa variant' but later named the Beta variant, 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 and remained under 1% since July 2021. The decrease was probably a result of the sharp increase of initially the Alpha variant, and later the Delta variant.</p> <p>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 (14). This appears to indicate that the variant caused more severe disease.</p>
	<p>Gamma variant. In the beginning of January 2021, another variant with S:K417N, S:E484K and S:N501Y mutations (501Y.V3 or variant P.1, lineage B.1.1.28) was detected in Japan in travellers arriving from Brazil (19). It was therefore initially referred to as the 'Brazilian variant', but was later named the Gamma variant. The variant only became predominant in some South American countries. In Belgium, its proportion in the baseline surveillance samples has fluctuated. In the period of 28 June-11 July 2021, it represented 6.3% of the baseline surveillance samples and its presence decreased thereafter to less than 1% because of the rise of the Delta variant.</p> <p>The study coordinated by the ECDC described above included 352 Gamma cases. Compared to non-VOC variant cases, Gamma cases had an adjusted odds ratio for hospitalisations of 2.6 (95 % CI: 1.4–</p>

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	<p>4.8) and for intensive care admission of 2.2 (95 % CI: 1.8– 2.9), suggesting that also this variant caused a more severe disease pattern (14).</p>
	<p>Delta variant. This variant was first detected in 2020 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 (20). It has mutations in the SARS-CoV-2 spike protein's coding sequence at E484Q and L452R and several other 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 a E484Q mutation. The Delta variant rapidly spread first in India and then in the UK, at a faster rate than previous variants (21), and it became the predominant variant worldwide during the summer of 2021. In Belgium, it became predominant at the beginning of July and universal in August. During the period September–November 2021 it represented almost 100% of the baseline surveillance samples. Mid-December 2021 its share decreased rapidly because of the emergence of the Omicron variant. In the period of 21 February to 6 March 2022 only one Delta sequence (0.2%) was reported. The Kappa variant was ever identified in few samples only.</p> <p>The Delta variant was about 40-60% more transmissible as the Alpha variant and around 95% more as the original Wuhan strain (22–24). Evidence from the UK showed a twice higher risk for hospitalization compared to the Alpha variant (25).</p> <p>There are several sublineages of B.1.617.2 (AY.1 to AY.41). Two of these sublineages (AY.4 and AY.23) seemed to have a relative advantage over the other AY sublineages worldwide. The AY.4 sublineage rapidly became dominant in the UK and the AY.23 sublineage in Singapore (26). A subdivision of AY.4 (AY.4.2) was considered by Public Health England as a variant under investigation (VUI) as it seemed to have a slightly higher transmissibility than the other sublineages (27). Its share slowly increased and it accounted at the beginning of November 2021 for about 15% of Delta cases in England (28). Preliminary analyses by PHE did not show any evidence of a difference in the risk of hospitalisation or death between AY.4.2 and other Delta sublineages, nor of a reduction in vaccine effectiveness (29). In Europe, the AY.4.2 sublineage was considered by ECDC as a variant of interest. In Belgium, the AY.4.2 sublineage was first detected in August 2021. By 14 November, 136 cases had been identified, still representing only a small proportion (<2%) of circulating strains. The AY.43 sublineage was more predominant and represented about 41% of circulating strains at that time (28).</p>
	<p>Omicron variant: On November 25, 2021, a new variant was reported by the South African National Institute for Communicable Diseases, lineage <u>B.1.1.529</u> (30). The variant raised concerns because of the large number and unusual constellation of mutations, with multiple mutations across the genome of which 30 in the spike protein (31). Some mutations were known to affect transmissibility and immune evasion (such as K417N, E484A, N501Y, T478K and P681H), but many others had been rarely observed. Similar to Alpha, the variant has S-Gene target failure (SGTF) and could therefore be detected by PCR assays using this target. Immune invasion, both for natural immunity from previous infections and for vaccine-induced immunity, was further confirmed by in-vitro neutralization studies and epidemiological data (see section on <u>Vaccine Effectiveness</u>). The variant was classified as a variant of concern by both ECDC (32) and WHO (33) on November 26, and named Omicron.</p> <p>Omicron had a large growth advantage over Delta, mainly because of the lesser susceptibility to existing immunity and because of certain epidemiological characteristics, such as a shorter incubation period and a larger proportion of asymptomatic, but highly infectious, infections. It very rapidly replaced Delta as dominant variant worldwide. By the end of December 2021 it represented 96% of all COVID-19 infections in the UK and 92% in Denmark, based on the proportion of PCR samples with SGTF (34,35). In Belgium, Omicron represented in the period of 21 February to 6 March 2022 99.8% of the positive samples in the baseline whole genome sequencing surveillance.</p> <p>Data from South Africa, the UK, Denmark, Canada and the US all show a lesser risk of hospitalization when infected with Omicron compared to Delta (34,36–39). In the UK, an analysis of a large number of Omicron and Delta cases showed that, after adjusting for age, vaccination status and re-infections, among others, the risk was about half of that for Delta (HR=0.53; 95%CI 0.50-0.57). In Canada, a similar analysis calculated a relative risk of 0.35 (95%CI 0.26-0.46) for hospitalization, and of 0.17 for</p>

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	<p>admission to intensive care. The duration of hospitalization is also shorter than for previous variants (40–44).</p> <p>BA.2 sub-lineage: The Omicron variant had initially been divided into four sub-lineages, BA.1, BA.1.1, BA.2 and BA.3 (45). Initially only the BA.1 sub-lineage rapidly spread worldwide, but the BA.2 sub-lineage quickly increased and replaced BA.1 (46,47). ECDC classified BA.2 as a Variant of Concern, separate from BA.1. In both Denmark and the UK, analyses show a significantly higher secondary attack rate amongst household contacts of BA.2 cases compared with BA.1 cases, indicating a higher infectuousness (48,49). In Denmark this is, however, only seen when the primary case is unvaccinated. A study in Qatar found that the viral load was significantly higher (Ct value on average 3.53 cycles lower) in BA.2 infections than in BA.1 infections (50). In Belgium BA.2 became the dominant sub-variant in February 2022. In the period 13–26 April 2022 it comprised 98–99% of all infections. Since then its share started to reduce, however, because of the emergence of new sub-variants (see below).</p> <p>The BA.2 sub-lineage has 16 specific mutations in the spike protein, compared to BA.1, and this raised concerns that it might behave different with regards to severity and susceptibility to immunity. The UKHSA had therefore classified it as a variant under investigation. There is, however, no evidence that supports these concerns (51). Two preliminary analyses from Denmark and the UK show no difference in severity compared to BA.1 (adjusted relative risk of hospitalisation of 1.06 (95% CI: 0.77–1.47) and 0.91 (95% CI: 0.85–0.98), respectively) (52,53).</p> <p>Recombinant variants: The Omicron and Delta variants co-circulated during a certain period, which created opportunities for recombinations. A first report from the University of Cyprus of such a recombinant variant at the beginning of January 2022 turned out to be a result of contamination in the lab, but in February 2022 actual recombinant variants were identified both in the UK and France (referred to as XF and XD, respectively). XF caused a small cluster in the UK (39 cases). XD was most prominent in France (40 cases) and one case was detected in Belgium (54,55). ECDC initially classified both recombinant variants as variant under monitoring (56), but de-escalated them later on because they were no longer detected.</p> <p>In addition, several recombinant variants of BA.1/BA.2 have been registered. At least two of these (XE and XK) have been detected in Belgium (57), but the numbers remained low. Only in the UK, XE appeared to be able to compete with BA.2 (58). Its share increased, although very slowly. In the period mid-April to end-May 2022 it comprised 1.2% of all sequenced samples (59).</p> <p>Other sublineages of Omicron: Several other sublineages of the Omicron variant with additional mutations have been described. Some of these mutations (such as S:L452R en S:F486V) have shown to be correlated with enhanced transmissibility and/or immune escape and therefore gave reason for concern. Two of these sublineages were first detected in South Africa and named BA.4 and BA.5. They rapidly overtook BA.2 as dominant sublineages in South Africa during April 2022, and caused a (relatively small) surge in new infections and hospitalizations. On May 12, 2022 ECDC classified them as variants of concern. BA.4 and BA.5 appear now also to outcompete BA.2 in Europe. In Portugal it became the dominant sublineage in May 2022, and is also there causing a (moderate) increase in infections and hospitalizations. Based on the presence of S-Gene target failure in PCR samples (which is present in BA.4/BA.5 and not in BA.2) the proportion of infections by BA.4/BA.5 in Belgium was estimated at 18–29% at the end of May 2022. It was expected to become the dominant sublineage during June 2022. In-vitro studies show a lesser susceptibility to antibodies generated by vaccination or previous infections than BA.2, which would explain their growth advantage (60–63).</p> <p>Also some sublineages of BA.2 have an additional mutation on S:L452. One of these (BA.2.12.1) rapidly overtook the other BA.2 sublineages as dominant lineage in the US and is believed to be contributing to an increase of new infections (64). ECDC classified for this reason all sublineages of BA.2 that have a mutation at the S position 452 (L452X) on the list of 'variants under monitoring'. However, BA.4 and BA.5 also emerged in the US and appear to be outcompeting BA.2.12.1.</p>
	<p>Other Variants. Another variant, characterized by the S13I, 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 was called</p>

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	<p>the <i>Epsilon variant</i>. The fast rise in their number and evidence of reduced neutralization by convalescent and post-vaccination sera (65,66) led initially to their classification as a VOC by the US CDC. However, it was later reclassified as a variant of interest (VOI) due to the significant decrease in the proportion nationally and available data indicating that vaccines and treatments were effective against this variant (67). The variant was mostly limited to the US and only one case has been detected in Belgium, where it is no longer considered a VOI.</p> <p>There are several variants of interest, but not of concern. One such variant is lineage <u>B.1.525</u> (sometimes referred to as the ‘Danish variant’, and now called the <i>Eta variant</i>). It carries the same E484K-mutation as found in the Beta and Gamma variants and was first detected in the UK in February 2021 (68). By June 27, 2021, 71 cases were described in Belgium. Another variant, first detected in Belgium and classified as VOI, is lineage <u>B.1.214.2</u>. (sometimes referred to as the ‘Congolese’ variant). It initially was detected in 4% of samples during March-April, but its prevalence then decreased. Outside Belgium it was rare and only considered as a variant under monitoring.</p> <p>A variant first detected in Columbia has lineage <u>B.1.621</u> and is classified as a VOI (called the <i>Mu variant</i>) (69). It only became very prevalent in Columbia and some other South-American countries, but was involved in a post-vaccination outbreak in Belgium with a significant proportion of fatalities. It was therefore actively followed-up by the NRC. However, the variant was not able to compete with the Delta variant and was therefore not a public health threat for Belgium (70).</p>
<p>Reservoir Last update 11 March 2022</p>	<p>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.</p> <p>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 phylogenetic studies are in favor of this hypothesis (71–73).</p> <p>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 (74,75). Research has not been able to identify with certainty which animal sold at the market was the intermediate host. A study analysing 1380 environmental and animal samples collected at the market in January 2020, did not obtain any positive result from 457 animal samples (76). The 73 PCR positive environmental samples confirmed, however, that the market was the origin of the pandemic. 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 (77). A combined genomic and geospatial analysis within the market showed that SARS-CoV-2-positive environmental samples were strongly associated with vendors selling raccoon dogs (78). One study using phylodynamic rooting methods, coupled with epidemic simulations, found evidence that there must have been at least two separate cross-species transmission events into humans (79).</p> <p>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 several other countries (80,81). 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 (82). 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 (83). In response, both the Netherlands and Denmark have culled all minks in the country.</p> <p>Various wild mammals, as well as cats and dogs, also have ACE2 configuration that is predicted to bind with SARS-CoV-2 S protein (84–87). Reverse zoonosis (disease transmission from humans to animals) is theoretically possible to all these animals and several such transmissions have already been documented (86,87). Of concern is that Omicron appears to bind more strongly to ACE2 than</p>

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	<p>other variants, which could increase the risk of reverse zoonosis (88). One animal in which SARS-CoV-2 has been extensively circulating and evolving is the North-American white-tailed deer (89–91). It shows that important reservoirs could be constituted in the wild, which evolve independently from the evolution in humans, and which also could be back-transmitted to humans.</p> <p>Adaptation in an animal reservoir, more specifically mice, and transmission back to human has been hypothesized as a possible origin of the Omicron variant, thereby explaining its large amount of mutations compared to previous variants (92,93). However, there are other plausible explanations, such as evolution in a remote area where nucleic acid tests are rarely conducted or evolution in immunosuppressed individuals with persistent infections, such as people living with HIV. The origin of Omicron remains therefore unsolved (94).</p>
<p><u>Physical and chemical resistance of the virus</u> <i>Last update</i> <i>15 May 2020</i></p>	<p>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). For more information on transmission through surfaces see the section on transmission.</p> <p>Like other coronaviruses, SARS-CoV-2 is very stable at 4°C but sensitive to ultraviolet rays and heat (inactivated within 5' at 70°). Furthermore, these viruses can be effectively inactivated by lipid solvents and common disinfectants including ether (75%), ethanol, chlorine-containing disinfectant, peroxyacetic acid and chloroform (96,97).</p> <p>Soap, which dissolves the lipid bilayer of the virus, also induces SARS-CoV-2 inactivation.</p> <p>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 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).</p>
<p>Prevention</p>	
<p><u>General public</u> <i>Last update</i> <i>03 September</i> <i>2021</i></p>	<p>General public For the general public, vaccination, handwashing, social distancing, avoiding crowded indoor spaces 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).</p>
<p><u>Community Masks</u> <i>Last update</i> <i>25 February 2022</i></p>	<p>Because of the possibility of asymptomatic and especially pre-symptomatic transmission face masks have been recommended. In addition to offering some protection to the wearer, they act 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). 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 (105–111).</p> <p>Evidence for the use of masks: The first evidence came from modeling data for Influenza suggesting that population-wide use of masks could importantly reduce spread of the virus (112–114). Lab-based experiments with SARS-CoV-2 clearly showed that the effectiveness of masks is greatest if they are worn by both the index case and the contact. In the same trials, cotton masks importantly lowered the amount of virus that was transmitted (111) as well as offered some protection against particles in the aerosol-range</p>

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(0.05 μ m) (115). In contrast to lab results, 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) (116) 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) (117). High-quality evidence for the universal use of masks in the community comes from a large cluster-randomized trial in Bangladesh including more than 300,000 individuals (118). In a random selection of communities, the use of masks was stimulated by distribution of free masks, in-person education on the usefulness of masks and other interventions. In those communities, correct mask use rose to 42.3%, as compared to 13.3% in the other communities. **The increase in mask use was linked to a decrease in persons reporting possible symptoms of COVID-19 (RR 11.9% p<0.01) and SARS-CoV-2 seroprevalence in those with symptoms (RR 9.3% p=0.043).** The decrease was larger for those villages with surgical mask use (reduction in symptoms 13.6% p<0.01) than for those with cloth mask use (8.5% p=0.048). Increased use of mask did not lead to a reduction in physical distancing.

Chronology of global mask mandates:

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 (119,120). ECDC listed a number of potential risks and benefits without either recommending or discouraging the use (121). A highly-influential review of the evidence compiled on April 10th 2020 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 (122). 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 (123). 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 2020. 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 (124). 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 (125).

Mask-wearing in children:

As outlined above, mask-wearing in adults has shown to be effective. Mask use in children remains more debated, as there are more uncertainties regarding benefit (eg. due to imperfect fit or low compliance) as well as potential harms (eg. by hindering communication) (125). Whilst many studies have shown that a combination of preventive measures in schools, including mask-wearing, reduces virus transmission (126–128), it is difficult to tease out the individual contribution of masks. A study from Georgia (US) end of 2020 showed a clear risk reduction for masking of teachers whilst masking might have been associated with a reduction in risk, but this was not statistically significant at the 0.05-level (RR 0.79 [0.50-1.08]) (129). Another study, from Arizona, found the odds of having a COVID-outbreak to be 3,5 times lower in schools that implemented mask policies (130). And, reassuringly, studies from France and the US have shown that even young children are able and willing to correctly wear masks (131,132).

On the other hand, mask-wearing might limit the ability to understand/hear the others and remove different visual cues that are necessary to communicate (131,132). Indeed, Gori et al. demonstrated in a trial presenting pictures of masked and unmasked people, that the mask may limit the ability of the children to properly understand emotions. The effect was particularly pronounced for children under 5 years old (133). In contrast, two other studies with a similar design did not find large differences in comprehension of emotions by children from 7 to 13 years when the face was partially covered (134,135).

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<p>Personal Protective Equipment Last update 04 February 2021</p>	<p>Health care workers WHO recommends the use of a surgical mask, gown, gloves, and goggles or faceshield for health care workers coming into close contact (<1,5m) with possible or confirmed cases of COVID-19 (136). During the SARS epidemic, adherence to these precautions was found to be effective to avoid infection in health care workers. The effect was largest for hand hygiene and use of masks (137).</p> <p>Surgical Masks vs. FFP2 Different health care authorities have issued different advice on the recommended PPE (138), which has led to confusion. Different types of masks exist: surgical masks or the more advanced 'respirators' like FFP2/3 (standard used in the EU) or N95 (standard used in the US). FFP2 masks sometimes come with an outlet valve, in which case they will only protect the individual wearing it but should never be given to a possible patient, as it will not protect the environment.</p> <p>In the above-mentioned trial during the SARS epidemic (137), 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 (139,140). This conclusion was confirmed by a meta-analysis including six RCTs published in March 2020 by the Chinese Cochrane Center (141). Some specific evidence for SARS-CoV-2 is also available from South Korea, where 41 health care workers were unknowingly exposed to <i>aerosol-generating procedures</i> 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 (142).</p> <p>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.</p> <p>Therefore, N95/FFP2 masks should be used preferentially for aerosol-generating procedures, such as endotracheal intubation and cardiopulmonary resuscitation (143). 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 (144) 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.</p> <p>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 (145). In addition, a few studies reported an increased risk of SARS-CoV infection associated with tracheotomy, noninvasive ventilation, and manual ventilation before intubation. However, because these findings were identified from only a few studies of very low quality, interpretation and practical application are difficult (146). 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: (138,147)</p> <ul style="list-style-type: none">• Intubation, extubation and related procedures
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	<ul style="list-style-type: none"> • 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). <p>Different authorities list different procedures (148). 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 (143,145,147).</p>
<p>Ventilation Last update 01 March 2022</p>	<p>Increased ventilation has been shown to reduce airborne transmission (149). In addition to increased ventilation, experts recommend limited room occupancy, avoidance of air recirculation (use 'extraction mode' for air conditioning) and frequent breaks (150–154). If recirculation of air is necessary, HEPA filters or MERV13 can filter sufficiently small particles (151). Two-and-a-half air changes have been reported to eliminate 90% of airborne contaminants (155). Opening doors and windows can generate up to 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...) (149,156).</p> <p>Use of a CO₂-sensor can help to assess whether ventilation is adequate or not. CO₂-levels should be kept below 800-1000ppm (157). This usually corresponds to the ventilation threshold set by WHO of 10 l/s/person (158). Technical guidance for maintenance of ventilation systems are available on the website of the Federation of European Heating, Ventilation and Air Conditioning Associations Very practical guidelines on how to assess and improve ventilation have been prepared by the Belgian Taskforce Ventilation: NL/FR.</p> <p>In two pre-print articles (not peer-reviewed and with several limitations), the effect of ventilation on the risk of infection is calculated on the basis of mathematical models. For example, Dai and Zhao state that at least 3-10 ACH are required to obtain a risk of infection of <1% during a half-hour bus ride with an infected person (159). Buonanno and colleagues calculated that in a fitness centre with a ventilation of 0.5 ACH the risk of infection is 1% after 55 minutes, whilst increasing ventilation to 3 ACH can prolong the 'safe' time to 110 minutes (160). Dai and Zhao emphasize that the use of mouth masks by both the index person and his contact person can drastically reduce the risk of contamination and thus the number of ACH required. A Dutch study modelled the effect of ventilation on infection in several situations (161). The authors conclude that the risk of airborne transmission is highest in certain crowded settings where people do intense activity, such as night clubs. Importantly, small improvements in very poorly ventilated spaces (from 'no ventilation' to 2l/s/p) would have proportionally a much larger effect than further improving already relatively good ventilation. Improving ventilation also reduces the risk of other respiratory viruses, in addition to SARS-CoV-2 (162)</p>
<p>Pre-exposure prophylaxis Last update 8 March 2022</p>	<p>Vitamin D There is a clear correlation between vitamin D deficiency and severe COVID-19 disease. A causal link has however not been shown. Only one small RCT assessed the use of vitamin D as adjunctive treatment in hospitalized patients, but numbers were too small to draw firm conclusions (163). Later reviews and meta-analyses conclude there is currently no evidence to recommend vitamin D supplements in primary prevention (163,164). Of course, any deficiency should be avoided, and therefore existing guidelines (update January 2021) for supplements in e.g. elderly people (800 IU vit D/d – 10 mg Zn/d) should be followed (165).</p> <p>Hydroxychloroquine Two randomized controlled trials published in the New England Journal of Medicine assessed the</p>

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	<p>use of HCQ as prophylaxis in individuals after a high-risk exposure of COVID-19 (166,167). Both trials did NOT find any benefit for HCQ but did find increased side effects.</p> <p>The website bcfi.be / cbip.be has a useful “COVID-19 update” section where recent information can be found.</p> <p>Monoclonal antibodies</p> <p>The FDA has approved the use of long-acting monoclonal antibodies tixagevimab and cilgavimab (Evusheld – AstraZeneca) by IM injections for pre-exposure prophylaxis of COVID-19 for the persons that are aged above 12 years old and weighting more than 40 kg. It is advised for patient that have a history of sever allergy that prevents vaccination against COVID-19 and/or are immunocompromised (168). It is the first drug that has been approved by the FDA for this indication and may protect against SARS-CoV-2 infection up to 6 months (169). PROVENT, an unpublished double-blind trial, included 5 172 patients that were randomized to either receive the treatment or the placebo. The study demonstrated a 77% reduction in the risk of being symptomatic amongst the group that received the treatment compared to the placebo (168). This treatment seems effective against the Delta variant but further data are needed to assess its effectiveness against Omicron variant (169).</p> <p>Belgian guidelines on the pre-exposure prophylactic use of antivirals are available in the section Patient Management.</p>
<p>Vaccination</p>	
<p><u>Vaccine development, authorisation and roll-out</u> <i>Last update</i> <i>4 March 2022</i></p>	<p>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) (170). According to the WHO COVID-19 candidate vaccine landscape (updated on 4 March 2022), 198 vaccines are in pre-clinical development and 163 vaccines are now in clinical development (86 in phase I or I/II, 30 in phase II or II/III, 36 in phase III clinical trials and 11 in phase IV).</p> <p>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 (mRNA vaccine; Comirnaty®), Moderna (mRNA vaccine; Spikevax®), AstraZeneca-Oxford (non-replicating viral vector vaccine, ChAdOx1; Vaxzevria®) and Johnson & Johnson (non-replicating viral vector, Ad26; COVID-19 Janssen vaccine®) and Novavax (recombinant spike protein vaccine, Nuvaxovid®). Full updates and key documents can be found on the EMA website. All have demonstrated high vaccine-efficacy (172–174). Other vaccines are currently in rolling-review.</p> <p>In addition to the EMA-authorized vaccines, the WHO emergency-use list includes the COVID-19 vaccines from Serum Institute of India (non-replicating viral vector vaccine, ChAdOx1-S; Covishield®) and recombinant spike protein vaccine, NVX-CoV2373, Covovax), Sinovac (inactivated adjuvanted vaccine, Vero Cell; CoronaVac®) , BIBP/Sinopharm (inactivated adjuvanted vaccine, Vero Cell; COVID-19 Vaccine BIBP), and Bharat Biotech's Covaxin® (inactivated adjuvanted vaccine, BBV152). Finally, the Gamaleya vaccine (viral-vector Ad26/rAc5 heterologous prime boost vaccine; Sputnik V (Gam-COVID-Vac)) (175), CanSino vaccine (viral vector Ad5), Vector Institute vaccine (“EpiVacCorona”, protein-based), Novavax (NVX-CoV2373 “Covovax”, protein-based) and the inactivated viral vaccine from Sinopharm-Wuhan have received conditional or emergency use authorisations in some countries and are being deployed in national vaccine campaigns across the world (NYTimes vaccine tracker). In August 2021, various media sources reported that an emergency approval was given by India to Zycov-D, a novel DNA COVID-19 vaccine.</p> <p>According to the WHO COVID-19 dashboard, over 11.9 billion COVID-19 vaccine doses have now been administered worldwide and almost five billion persons have been fully vaccinated. Country profiles with regards to COVID-19 vaccine roll-out and uptake are published by the WHO. The ECDC vaccine tracker also gives and overview of vaccine roll-out in Europe.</p>

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	<p>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 pregnant women), before being expanded to the general population. Comirnaty®, SpikeVax®, Nuvaxovid® and Janssen’s COVID-19 Vaccine® are in use, while Vaxzevria is not frequently used anymore since summer 2021. In September 2021, an additional mRNA dose to complete the primary vaccine schedule (as opposed to a true booster-dose) was recommended in immunocompromised persons.</p> <p>Since October, mRNA booster doses are being offered to residents of MR/MRS and people aged 65 and over. In November, also healthcare workers, and people who have received one dose of Janssen’s COVID-19 Vaccine® were offered a mRNA booster dose. Since December the whole 18+ population was invited to receive booster doses with a minimal interval of two months after Janssen’s COVID-19 Vaccine® and four months for the other vaccines. Since end December, a primary vaccine is offered to children aged 5-11 years using a paediatric formulation of the Comirnaty® vaccine with a reduced dose of mRNA. The Novavax vaccine, was approved for use in Belgium in January 2022 and is primarily offered to individuals who have a high risk of allergic reactions against others vaccines used in the Belgian vaccination campaign and for those who have already experienced a severe side effect after vaccination. Since February booster doses are being offered also to adolescents between 12 to 17 years in Flanders on a voluntary basis and under parental consent. Since the 4th of March 2022 the booster campaign has been extended to 12-17 year-olds with high risk. Additionally, since February, an additional booster dose is offered to people who have received a primary schedule with the COVID-19 Vaccine® Janssen, at least 3 months after a first one, on a voluntary basis.</p> <p>Since end January, a second booster dose was recommended for immunocompromised persons, at least three months after the additional dose. In Flanders, a second booster vaccination is currently being offered to people staying in nursing home and individuals older from 80 years old.</p> <p>The countries’ vaccine uptake and coverage can be followed on the national dashboard epistat, and additional information can be found in our FAQ surveillance and https://covid-19.sciensano.be/fr/covid-19-vaccination.</p>
<p>Vaccine effectiveness <i>Last update</i> 24 February 2022</p>	<p>Many studies have by now published vaccine effectiveness (VE) results (set in “real-life settings” as opposed to clinical trials). Most of these studies have generally showed a good protection against infection (all or symptomatic) (176–199), hospitalization (177,179,184,186,193,197,199–201) and death (130,132,139,147,150). Protection by mRNA vaccines (Comirnaty® and especially Spikevax® (Moderna)) appears to be somewhat better than by non-replicating viral vector vaccines (Vaxzevria® and Janssen® (Johnson & Johnson)), especially against infection. Protection against the Alpha and Delta variants did not differ substantially from that against the original strain, although that protection against asymptomatic infection and transmission by Delta appeared to be somewhat lower. Protection against infection (both asymptomatic and symptomatic) by the the Omicron variant (both BA.1 and BA.2 sublineages), however, is substantially less than against previous variants and wanes more rapidly. Protection against hospitalization appears to be good, similar or only slightly lower to that against hospitalization by previous variants, but wanes relatively more rapidly.</p>
	<p>Pre-Delta era (Wuhan and Alpha variants)</p> <p>A systematic review by Harder et al of 30 studies conducted before mid-May 2021 looked at the VE of EMA-approved vaccines. First-dose VE against SARS-CoV-2 infection was investigated in 26 studies and ranged from 16.9% to 91.2%, with the majority of estimates ranging between 60% and 70%. VE estimates after the second dose ranged between 61.7% and 98.6% (17 studies included), with the majority of estimates ranging from 80% to 90%. VE against asymptomatic infection after one dose of Comirnaty® or Spikevax® ranged from 36% to 79%, and after a second dose from 80% to 94%. For the single-dose regimen of COVID-19 vaccine Janssen®, VE against asymptomatic infections was 74% in one RCT (203). A systematic review and meta-analysis of 8 studies, specifically looking at VE of Comirnaty® against COVID-19 infection (regardless of symptoms), found 53% (95%CI</p>

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	<p>32–68) VE 14 days after the first dose and 95% (95%CI 96-97) 7 days after the second dose (204). Another systematic review looked at 11 studies and concluded that, although data availability was limited, the studies suggest equivalent effectiveness of Comirnaty® and Vaxzevria® against SARS-CoV-2 infection and COVID-19 related morbidity and mortality, which increased with time and a second dose (205).</p> <p>An estimate of VE in Belgium was done through an analysis of the contact tracing data. During the period January-June 2021, VE against infection for a fully vaccinated HRC and an unvaccinated index was estimated at 74% (95%CI 72–76) for Comirnaty® and 85% (95%CI 80–90) for Spikevax®. For the viral-vector vaccines Vaxzevria® (53%; 95%CI 12–84) and Janssen® (61%; 95%CI 29–84), the numbers were too small and the 95%CIs too large to draw real conclusions (206).</p>
	<p>Beta and Gamma variant</p> <p>The Beta and Gamma variants raised concerns about vaccine effectiveness due to the presence of the E484K escape mutation. These concerns were further increased by several laboratory studies suggesting a reduction in neutralizing capacity against the Beta variant of Comirnaty® or Spikevax® elicited antibodies (207–213), Vaxzevria® elicited sera (210,214) and sera from Janssen® vaccinees (215,216). Data with regards to the neutralizing capacity against the Gamma variant were more reassuring (210,217). With regard to Janssen®, laboratory studies suggested a 3.3 to 3.6-fold reduction in neutralizing capacity of J&J vaccinees’ sera (215,216), but CD8 and CD4 T cell responses seemed to not be affected (216).</p> <p>Doubts about the VE of Vaxzevria® were raised after a South African study found a very low effectiveness of 10.6% (95%CI:-66.4 to 52.2) of two doses of Vaxzevria® against mild to moderate laboratory confirmed COVID-19 (218). These results led to the South African decision to halt the vaccine roll-out of Vaxzevria®. However, the dose interval was only 21-35 days (219), which is substantially lower than the 12 weeks used in Belgium.</p> <p>With regards to Comirnaty®, a study in Qatar showed a 15% lower VE ≥ 14 days after the second dose of Comirnaty® against the Beta variant than against the Alpha variant (220,221). In addition, an Israeli pre-print found that breakthrough cases, 7-13 days after the second dose, were disproportionately infected with Beta as compared to non-vaccinated cases (odds ratio 8:1), suggesting a possible reduced vaccine effectiveness (222).</p> <p>A Canadian pre-print showed minor reductions in VE against symptomatic infection with the Beta and Gamma variant as compared to the Alpha variant after 2 doses of Comirnaty® (84% vs. 89%) and after 1 dose (60% vs. 66%), but no reduction in protection against hospitalisation or death (199).</p>
	<p>Vaccine effectiveness against Delta variant</p> <p>The VE against the Delta variant has been well documented by real-life observational studies. Interim results of a living systematic review and meta-analysis of 17 studies (223), showed a VE against any infection ranging between 49% and 82%, and a pooled VE of 66.9% (95%CI: 58.4–73.6) (224–233). Against asymptomatic infection VE ranged between 35.9% and 80.2% and the pooled VE estimate was 63.1% (95%CI: 40.9–76.9) (227,232); against symptomatic infection it ranged between 56% und 87.9%, and the pooled VE was 75.7% (95%CI: 69.3–80.8) (199,224,227,228,232,234–237); and against severe disease and hospitalization it ranged between 75% and 96%, and the pooled VE was 90.9% (95% CI: 84.5–94.7) (229,230,232,233,237–239). In nine studies, VE estimates against infections with the Delta variant were compared with those against infections with the Alpha variant. Overall, VE against Delta was 10–20% lower than VE against Alpha for less severe outcomes. For hospitalization, VE against Delta did not differ from VE against Alpha. Heterogeneity was high among studies assessing mild to moderate forms of COVID-19 ($I^2 > 90\%$), but low among studies assessing severe outcomes ($I^2 = 18\%$), further supporting a well-maintained effectiveness against severe disease under Delta variant dominance.</p>

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Vaccine effectiveness against Omicron variant

In-vitro neutralization studies, including one by the NRC, confirmed the potential for immune invasion, both for natural immunity from previous infections and for vaccine-induced immunity (240–243).

The evasion of existing immunity was further confirmed by epidemiological data from several countries. In the UK and South Africa, there was a marked increase in overall reinfection rates, even after adjusting for the size of the previously infected population (34,244).

In the UK, a test-negative case-control analysis showed a substantially less effectiveness of primary vaccination (two doses) against **symptomatic infection** by Omicron than by Delta, that also waned more rapidly over time (245). The same was observed after booster vaccination. Among those who received Vaxzevria[®], VE was around 60% 2 to 4 weeks after a Comirnaty[®] booster and around 70% after a Spikevax[®] booster, then dropped to 40% by 10 weeks with both booster vaccines, and to 30% with a Comirnaty[®] booster after 15 weeks. Among those who received a Comirnaty[®] primary course, VE was around 70% after a Comirnaty[®] booster, dropping to 40% after 15-plus weeks, and dropped from 75% 2-4 weeks after a Spikevax[®] booster to 60% up to 10-14 weeks after the booster. A similar analysis in Canada found that 2 doses of COVID-19 vaccine (of which at least one was an m-RNA vaccine) was not protective at any point after vaccination against Omicron **infection**, while against Delta it was 84% in the first months after vaccination, declining to 71% after 8 months (246). VE increased again from ≥ 7 days after receiving an mRNA booster to 37% (95%CI, 19-50%) against Omicron infection and to 93% (95%CI, 92-94%) against a Delta infection.

VE after booster vaccination against **hospitalization** was assessed in two studies in the UK (247). In a large study analyzing more than 500,000 Omicron cases, VE against hospitalization was 81% (95%CI 77-85%). In another, smaller study analyzing only symptomatic cases it was 68% (95%CI 42-82%). Combined with the protection against becoming a symptomatic case, this gave a VE against hospitalisation of 88% from 2 weeks after booster dose (95%CI 78 to 93%). However, also VE against hospitalization wanes over time. The test-negative case-control analysis in the UK found that VE against hospitalization after booster vaccination with Comirnaty[®] declined from about 90% after one week to less than 80% after 10-14 weeks among those who received Vaxzevria[®] primary vaccination, and from about 90% after two weeks to about 75% after 10-14 weeks among those who received Comirnaty[®] primary vaccination (245).

Analysis in the US of 241,204 emergency department/urgent care encounters and 93,408 hospitalizations calculated that during the Omicron period, VE against ED/UC visits was 87% during the first 2 months after a third dose and decreased to 66% among those vaccinated 4-5 months earlier; VE against hospitalizations was 91% during the first 2 months following a third dose and decreased to 78% after ≥ 4 months (248).

The test-negative case-control analysis in the UK estimated the VE against **mortality** for those aged 50 years and older by combining the risk of becoming a symptomatic case with the risk of death among symptomatic cases. At 25+ weeks following the second dose (all vaccines combined), VE was around 60% while at 2 or more weeks following a booster vaccine effectiveness was 95% (245).

Preliminary data from the UK on VE against the **BA.2 sublineage** shows a similar level of protection as against the BA.1 sublineage (249). After 2 doses effectiveness against symptomatic disease was 10% (9 to 11%) and 18% (5 to 29%) respectively for BA.1 and BA.2, after 25+ weeks. This increased to 69% (68 to 69%) for BA.1 and 74% (69 to 77%) for BA.2 at 2 weeks following a booster vaccine before decreasing to 49% (48 to 50%) and 46% (37 to 53%) respectively after 10+ weeks. In Qatar, a similar analysis found that VE in the first month after a Comirnaty[®] booster dose was 59.9% (95% CI: 51.2-67.0%) against symptomatic BA.1 infection and 43.7% (95% CI: 36.5-50.0%) against symptomatic BA.2 infection (250). Effectiveness against COVID-19 hospitalization and death was in

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	<p>the range of 70-80% any time after the second dose, and was greater than 90% after the booster dose. Similar patterns of protection were observed for the Spikevax[®]vaccine.</p>
	<p>Vaccine effectiveness in the elderly and in residents of long-term care facilities</p> <p>If VE has been found to decline mildly but significantly with age (183), several studies have shown that high effectiveness is still achieved in the elderly (177,179,186,200,201,251). The systematic review by Harder et al summarized above (pre-Delta period) found that first-dose efficacy against infection was lower in older (e.g. long-term care facility inhabitants) than in younger participants (e.g. healthcare workers), but VE after full vaccination was not affected by participant age (203). A first large VE study in Israel found estimates in individuals of 70 years and older to be very similar to those in younger age groups, after the second dose (179). A second Israeli study found a slightly lower effectiveness against symptomatic COVID-19 in individuals of 65 years and older, when compared to younger age groups (186). 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 and to a much lesser extent for two doses (193). In a large English study effectiveness against symptomatic infection among ≥80 years old was 89% 14 days after the 2nd dose of Comirnaty[®] (177). However, some studies do report on substantially lower effectiveness in elderly. The above mentioned Scottish study, focussing on VE against hospitalisation, found that VE was lower in the ≥80 years age group than in younger age groups: 83% (95%CI 72-89) vs. 93% (95%CI 73-98) in the 65-79 years old and 92% (95%CI 82-97) in the 18-64 years old (200). Also a Brazilian study found a lower protection in the most elderly during the predominance of the Gamma variant, although that this was after vaccination with CoronaVac (Sinovac Biotech). VE against symptomatic COVID-19 ≥14 days after the second dose was 59% among the 70-74 years old compared to only 33% among the ≥80 years old, and similar differences were observed for protection against hospitalisation and death (252). In the study among veterans in the US (see above), protection by either Comirnaty[®] or Spikevax[®] against hospitalization was significantly lower among ≥65 years old (79.8%; 95%CI 68-87) than among 18-64 years old (95.1%; 95%CI = 89.1%–97.8%) (253), and in the study among general hospitalized patients a similar result was observed (76% (64–84) in ≥75 years old and 89% (85–92) in 18-74 years old) (254).</p> <p>A Danish pre-print found a lower VE by Comirnaty[®] against infection >7 days after second dose in nursing home residents (64%; 95%CI 14–84) than in health care workers (90%; 95%CI 82–95) (182). 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 (255). 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 (197). 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 (256). The finding was in agreement with the results of the SCOPE study, that monitors the sero-prevalence of SARS-CoV-2 among residents and staff in Belgian nursing homes. In the second testing round (March-May 2021), 99% of fully vaccinated staff had anti-SARS-CoV-2 antibodies, while only 91% of fully vaccinated residents had. Among those with a history of infection, the proportion was similar among residents and staff (257). This suggest that perhaps adapted vaccination regimens are needed in this vulnerable population. Results from laboratory studies should be interpreted with caution though, since no correlate of protection has been defined yet.</p>
	<p>Vaccine effectiveness in immunocompromised patients</p> <p>Several studies have shown a reduced immunologic response to COVID-19 vaccination among people with various immunocompromising conditions. Compared with those who are not immunocompromised, reduced antibody response to two doses of mRNA vaccines has been observed in specific groups of immunocompromised adults, including people receiving solid organ</p>

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	<p>transplants (258–263); people with cancer, particularly hematologic cancers (264,265); people receiving hemodialysis for kidney disease (266,267); and people taking certain immunosuppressive medications (260,262,263). While antibody measurement and threshold levels varied by study and there is still debate on the level to be used as correlate of protection, a large proportion of immunocompromised persons overall had a measurable immune response, although some remained seronegative.</p> <p>In addition, some studies found a significantly lower vaccine effectiveness among immunocompromised adults compared to those without immunocompromising conditions, although each study defined the immunocompromised population differently (268–270). Studies in the US and Israel have also found that immunocompromised persons account for a high proportion ($\geq 40\%$) of infections among fully vaccinated hospitalized persons (270,271).</p>
	<p>Vaccine effectiveness in children and adolescents</p> <p>Phase 2/3 placebocontrolled clinical studies established that the neutralizing titers increased substantially after 2 doses of an m-RNA vaccine (Comirnaty® and Spikevax®) in both adolescents and children, and more than in young adults (range 16-25 years) (272–275). The clinical trials of Comirnaty® in children aged 5-11 years and in adolescents 12-15 years have reported VE against COVID 19 infection of 90.7% (95% CI 67.7 to 98.3) and 100% (95% CI, 75.3 to 100), respectively (273,276). One of these studies specifically assessed neutralization capacity against the Omicron variant (275). It found that in adolescents and children the elicited neutralization responses against Omicron were reduced compared with the Wuhan strain. However, the neutralizing capacity was still 3.8-fold higher in adolescents (12-17 years) and 2.5-fold higher in children (6-11 years), than in adults.</p> <p>Observational studies confirm a strong protection by Comirnaty® against infections with the Delta variant. A retrospective cohort study in Israel calculated a VE against infection among adolescents 12-15 years old, without a history of previous infection, in the third week after administration of the second vaccine dose of 91.2% (87.4%–93.8%) (277). A similar study in South Korea among adolescents 16-18 years old measured a VE against infection of 99.1% (95% C.I. 98.5–99.5) 14 days post-second dose (278). In a test-negative case-control study in the US, VE against hospitalization was 94% (95% CI, 90 to 96) and against ICU admission 98% among adolescents 12-18 years old (279).</p> <p>As for vaccination in adults, the effect in adolescents wanes over time. In a matched case-control study in Israel among adolescents 12-16 years old, VE against infection (regardless of symptoms) decreased from 85% between 2 weeks and 3 months after the second dose to 75% 3 to 5 months after the second dose and to 58% after 5 months. For VE against symptomatic infections the figures were 90%, 78% and 65%, respectively (280).</p> <p>No observational studies have yet assessed VE in adolescents or children against the Omicron variant.</p>
	<p>Effect on transmission</p> <p>Vaccination not only reduces the risk of a person becoming infected, but can also reduce the infectivity of a person, if infected, and thus the risk of that person infecting others. Several studies assessed the effectiveness of vaccination in preventing further transmission to contacts. Studies in the UK, Israel and the Netherlands all documented a lower risk of infection among household contacts of vaccinated index cases than of unvaccinated (184,281–284).</p> <p>The analysis of the contact tracing data in Belgium for the period January-June 2021 showed that onwards transmission from a fully vaccinated index case to the high-risk contacts was reduced by 62% (95%CI 57–67) for Comirnaty® and 52% (95%CI 33–69) for Spikevax®. A reduction was also seen for Vaxzevria® and Janssen®, although less strong and not statistically significant at the 95% level because of lower numbers (206).</p> <p>Some studies assessed impact on transmission during the Delta era and found a lower VET to household contacts during the Delta era compared to the Alpha era (285,286). One study found</p>

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	<p>that the secondary attack rate among household contacts exposed to fully vaccinated Delta index cases was similar to household contacts exposed to unvaccinated index cases (287).</p> <p>Data on the VET of the Omicron variant are still scarce. A Danish study found in the period that both Delta and Omicron were circulating, an increased household transmission for unvaccinated index cases (odds ratio of 1.4 (95%CI 1.3-1.6)) and a reduced transmission for booster-vaccinated index cases (odds ratio of 0.7 (95%CI 0.6-0.9)), compared to fully vaccinated index cases without booster. They report no substantial difference in VET between households with an Omicron index case and households with a Delta index case, and therefore expect no inherently increased transmissibility of the Omicron variant (288). The same authors compared household transmission by index cases infected with the BA.1 and the BA.2 Omicron sublineages (49). They observed lower transmissibility in both BA.1 and BA.2 households when the primary case was booster vaccinated rather than fully vaccinated. Transmissibility in BA.2 households from unvaccinated primary cases was higher compared to BA.1 households, but lower for fully vaccinated and booster-vaccinated primary cases, where the estimates were below 1 for BA.2 compared to BA.1 (OR 0.60, 95%CI 0.42-0.91, and OR 0.62, 95%CI 0.42-0.91, respectively).</p>
	<p>Mixed dose schedules</p> <p>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, despite limited data regarding the safety and immunogenicity of these mixed dose schedules at that time. Several observational studies and one RCT found, since then, mixed dose schedules to have a comparable safety profile as normal (or homologous) schedules (289–293). The available laboratory evidence is suggestive of an at least equal or slightly better immune response after a mixed dose schedule as compared to a homologous prime-boost schedule (289,290,292,294–299). One study measured vaccine effectiveness against SARS-CoV-2 infection when combining the first dose of Vaxzevria® with a second dose of an mRNA vaccine and found a similar VE (88%) as compared to two doses of an mRNA vaccine (300). ECDC concluded that heterologous schedules may offer flexibility in terms of vaccination options, while further research is ongoing to provide more evidence on long-term safety, duration of immunity and effectiveness. A systematic review that included 10 articles concluded that vaccination with Vaxzevria®/Comirnaty®, Vaxzevria®/Spikevax® or Comirnaty®/Vaxzevria® did not have the serious adverse events seen with homologous vaccination, and showed a more robust immune response against SARS-CoV-2 (301).</p> <p>One clinical trial in the US assessed safety, reactogenicity and humoral immunogenicity after a booster injection with one of three vaccines (Spikevax®, Janssen® or Comirnaty®) in people who had been fully vaccinated at least 12 weeks prior to enrollment with either of these vaccines (9 possible combinations). Homologous and heterologous booster vaccinations were well-tolerated and homologous boost increased neutralizing antibody titers against a D614G pseudovirus by 4.2-20-fold whereas heterologous boost increased titers 6.2-76-fold (302). In general, day 15 titers post-boost were highest in Spikevax®-primed participants, followed by Comirnaty® and Janssen®, irrespective of the booster. Persons who received an mRNA-based booster vaccination had a four-fold increase in their neutralization response more frequently than those who were boosted with Janssen®.</p>
	<p>Duration of protection</p> <p>Several large-scale retrospective analyses of health records have documented a progressive waning in VE against infection (asymptomatic or symptomatic) over time, but to a lesser degree for VE against severe disease or deaths (303–307).</p> <p>A large retrospective cohort study in the US found that VE of Comirnaty® against SARS-COV-2 infections (all variants) declined from 88% during the first month after full vaccination to 47 after ≥5 months (304). Against Delta infections, VE was high during the first month after full vaccination (93%) but declined to 53% at ≥4 months. Protection against COVID-19-related hospitalization did not wane over time, with overall adjusted VE estimates of 87% at < 1 month after being fully vaccinated, and 88% at ≥5 months after full vaccination. The decline was observed across age groups.</p> <p>In a matched test-negative, case-control study in Qatar, VE of Comirnaty® reached its peak at 78% in the first month after the second dose and declined gradually thereafter, with the decline</p>

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	<p>accelerating after the fourth month to reach approximately 20% in months 5 through 7 after the second dose (305). Effectiveness against symptomatic infection waned in the same fashion. Effectiveness against any severe, critical, or fatal disease reached 96% in the first 2 months after the second dose, where it persisted at about this level for six months. Similar patterns were seen for Alpha, Beta and Delta infections.</p> <p>A similar analysis of UK data, showed that VE against symptomatic disease peaked in the early weeks after the second dose then fell to 47% and 70% by 20+ weeks against the Delta variant for Vaxzevria® and Comirnaty®, respectively (306). Waning of VE was greater among 65+ year-olds compared to 40 to 64 year-olds. There was limited waning in protection against hospitalization, with a vaccine effectiveness of 77% and 93% beyond 20 weeks post-vaccination for Vaxzevria® and Comirnaty®, respectively (Delta only). Similarly, there was limited waning of vaccine effectiveness against deaths Vaxzevria® (VE 79%) and Comirnaty® (VE 90%) beyond 20 weeks post-vaccination for all ages.</p> <p>Finally, a retrospective matched cohort study in Sweden found that VE of Comirnaty® against infection waned progressively from 92% at day 15-30 to 47% at day 121-180, and to 23% from day 211 and onwards (307). The VE waned slightly slower for Spikevax®, estimated to be 59% from day 181 and onwards. In contrast, VE of Vaxzevria® was generally lower and waned faster, with no effectiveness detected from day 121 and onwards (-19%), whereas VE from heterologous Vaxzevria®/ mRNA was maintained from 121 days and onwards (66%). Overall, VE was lower and waned faster among men and older individuals. For the outcome severe Covid-19, VE waned from 89% at day 15-30 to 42% from day 181 and onwards, with sensitivity analyses showing notable waning among men, older frail individuals, and individuals with comorbidities.</p> <p>Waning of immunity has further been demonstrated in several studies assessing the evolution of SARS-CoV-2 antibodies since time of vaccination (308–310).</p> <p>Waning over time is still more important for immunity against the Omicron variant, as is described in the section VE against the Omicron variant.</p>
	<p>Additional dose</p> <p>Data from small observational studies suggested that an additional mRNA vaccine dose in <i>immunocompromised people</i>, typically administered at least 28 days after completion of the primary vaccination, increases antibody response in solid organ transplant recipients (311–314) and hemodialysis patients (315–317). An important proportion (about 50%) of those who had no detectable antibody response to the initial two-dose series developed an antibody response to the additional dose. An RCT demonstrated substantial increases in serologic immune response to a third dose of Spikevax® compared with placebo among solid organ transplant recipients (318). The clinical impact of an additional dose on acquisition, severity, and infectiousness of infections in fully vaccinated immunocompromised persons is not yet completely understood, but most international agencies and Western countries, including Belgium, already recommend it.</p> <p>Evidence on the effectiveness of an additional booster dose in other populations than immunocompromised people is still limited, but increasing. Some RCTs and observational studies in pre-print show an increase in geometric mean titers (GMTs) of neutralizing antibody after an additional dose, several months after completing the initial doses of Comirnaty® (319) or CoronaVac (320,321).</p> <p>Real world data of the effect of the third dose of Comirnaty®, 5 months or more after the the second dose, became first available from Israel and the UK.</p> <p>In Israel, among ≥60 years old, non-booster recipients had a 11.3 higher risk for infection and a 19.5 higher risk for severe disease compared to booster recipients (322). An analysis across all age groups showed a ≈10-fold lower infection rate in the booster versus nonbooster group, with similar rates across age groups: 12.4 for people 60+ years of age, 12.2 for people aged 50-59, 9.7 for people aged 40-49, 8.8 for people aged 30-39, and 17.6 for people aged 16-29 (323). The severe illness rate was 18.7-fold lower for ages 60+, and 22.0-fold lower for ages 40-60. For ages 60+, COVID-19 associated death rates were 14.7-fold lower in the booster group. A case-control study among healthcare services clients calculated a 48-68% reduction in the odds of testing positive for SARS-CoV-2 after 7-</p>

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	<p>13 days and 70-84% 14-20 days after the booster compared to two doses (324). Another retrospective analysis of healthcare service client records calculated a VE of 93% against hospitalization; 92% against severe disease; and 81% against COVID-19-related death (325).</p> <p>In the UK, among >50 years old, VE against symptomatic infection of a booster dose relative to those who only received two doses was 87.4% for those previously vaccinated with Vaxzevria® and 84.4% for those vaccinated with Comirnaty®. Compared to unvaccinated individuals, the absolute VE against symptomatic infection was 93.1% for those previously vaccinated with Vaxzevria® and 94.0% for those vaccinated with Comirnaty®.</p> <p>The evidence on booster dose effectiveness is also supported by the evidence with regards to waning of vaccine-induced immunity in time (see above).</p> <p>In October 2021, the EMA's human medicines committee approved the use of a booster dose of Comirnaty® or Spikevax® at least 6 months after the second dose in people aged 18 years and above. For Spikevax®, the booster dose consists of half the dose used for the primary vaccination schedule.</p> <p>The first data on the effectiveness of a fourth dose are coming from Israel. In a clinical intervention trial, recipients of either Comirnaty® or Spikevax® fourth dose had a ~9-10-fold increase in IgG and neutralizing titers within 2 weeks of vaccination and an 8-fold increase in live Omicron VOC neutralization, restoring titers to those measured after the third vaccine dose (326). Vaccine efficacy against infection (whether symptomatic or not) was 30% (95%CI:-9% to 55%) and 11% (95%CI:-43% to +43%) for Comirnaty® and Spikevax®, respectively, compared to individuals who received the third dose of the full Comirnaty® schedule, at least 4 months earlier. An observational case-control study assessed the effect of a fourth dose of Comirnaty® in people aged over 60 years and at-risk populations (327). The rate of infection was twice (95%CI: 2.0 to 2.1) lower 12 or more days after the fourth dose than among those who received only three doses. The rate of severe illness was lower by a factor of 4.3 (95% CI, 2.4 to 7.6), compared to those who received only three doses.</p>
	<p>Hybrid immunity</p> <p>Several in-vitro neutralization studies have shown that the capacity to neutralize Omicron by sera from individuals who were vaccinated and previously infected with SARS-CoV-2 was several times higher than that by sera from vaccinated individuals with no evidence of previous infection (328–330).</p> <p>The additional protective effect of a combined prior infection/vaccination, compared to only a prior infection or vaccination, has also been observed in real-life. For example, a study in Qatar, during the periods that the Beta and Delta variants were dominant, calculated that the risk for infection after a Comirnaty®-vaccination was 5.5 times lower among individuals with a prior infection than among individuals without (Adjusted HR=0.18 [95% CI, 0.15-0.21]) (331). After Spikevax®-vaccination the risk was 3 times lower (AHR=0.35 [95% CI, 0.25-0.48]). Preliminary analysis of data of the British SIREN study, showed that prior infection offered 44% protection against Omicron infection, compared to 32% for 2-dose vaccination and 62% for booster vaccination (332). Protection by a combined prior infection and 2-dose vaccination was similar to that of booster vaccination (60%), and of a combined prior infection and a booster vaccination it was 71%.</p>
<p>Vaccine safety Last update 20 September 2021</p>	<p>Phase III clinical trials allow the identification and characterisation of the common side-effects of each vaccine. These are usually benign, ranging from headaches to fever, are summarized in the medicine's agency AFMPS/FAGG FAQ and in the package leaflet when the vaccine is marketed.</p> <p>In addition, to ensure the detection of rarer or late-onset adverse effects, post-marketing surveillance of vaccine safety is organized, both at European level (EMA) and national level (AFMPS/FAGG). EMA publishes regular reports on vaccine safety profiles. Belgium's national vaccine-safety data is available in a monthly bulletin published on the medicine's agency AFMPS/FAGG website. Here we summarise the severe safety signals that have been identified through post-marketing surveillance as COVID-19 side effects. The frequency category allocated to most of the side-effects described below is 'very rare' (i.e. occurring in less than 1 in 10,000 persons), which is the category of the lowest frequency foreseen in EU product information. Health</p>

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professionals should be aware of these side effects for early recognition and adequate management. For all groups in which the Superior Health Council advised the vaccine, benefits of vaccination are estimated to largely outweigh the risks of severe adverse events.

Thrombosis with Thrombocytopenia Syndrome (TTS) ;

- Very rare side effect of viral-vector vaccines 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 splanchnic vein thrombosis, but also arterial vein thrombosis) and thrombocytopenia. Most of the reported cases have occurred within the first three weeks following vaccination. The majority of cases have been reported in individuals under 60 years of age, although biases such as underreporting in older age groups is possible. The overall case fatality rate is 17% and significantly lower incidence is found after the second dose compared to the first dose in the younger recipients ([weekly UK MHRA report](#)).
- The exact physiopathology behind this syndrome is yet to be confirmed, but one of the leading hypothesis is that of an atypical heparin-induced thrombocytopenia-like syndrome, involving the production of platelet-activating anti-PF4 antibodies (333,334).
- Diagnostic work-up and management of such cases has been proposed by the [Belgian Society on Thrombosis and Haemostasis](#). Individuals diagnosed with thrombocytopenia within three weeks after vaccination with Vaxzevria/ COVID-19 Vaccine Janssen, should be actively investigated for signs of thrombosis. Similarly, individuals who present with thrombosis within three weeks of vaccination should be evaluated for thrombocytopenia. The guidance emphasizes 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.

Severe allergic reactions

- mRNA vaccines Comirnaty® and Spikevax® : although still very rare, severe allergic reactions including anaphylaxis have occurred at a higher rate than predicted by clinical trials or than what is usually observed with non-COVID vaccines. 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.
- Vaxzevria® and COVID-19 Vaccine Janssen® : Cases of anaphylaxis have also been reported. These vaccines do not contain PEGs but does contain the related compound polysorbate 80.
- A pragmatic document to assess allergy 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

- Very rare side effect of viral-vector vaccines Vaxzevria® and COVID-19 Vaccine Janssen®.
- A rare and severe disorder characterised by massive leakage of plasma from blood vessels into adjacent body tissues. Capillary leak syndrome results in swelling mainly in the arms and legs, low blood pressure, thickening of the blood and low blood levels of albumin.
- Vaxzevria® and COVID-19 Vaccine Janssen® are contraindicated in persons with a history of capillary leak syndrome.

Myocarditis and pericarditis :

- Very rare side effect of mRNA vaccines Comirnaty® and Spikevax®
- Cases occur primarily within 14 days after vaccination and more often after the second dose and primarily in male adolescents aged 16 years or older. Acute clinical courses have been generally mild. (335).
- In October 2021, various public health institutions in Nordic countries (e.g. Sweden, Finland, Norway, Iceland) either paused the use of Spikevax® or made preferential recommendations for the use of Comirnaty® rather than Spikevax® in younger people and/or younger males. These recommendations were based on preliminary results of an unpublished Nordic study using population-based register data on myocarditis and

pericarditis. A pharmaco-epidemiological study from France ([link](#)) has also concluded on an infrequent risk of myocarditis and pericarditis within 7 days of vaccination with Comirnaty or Spikevax in people aged 12 to 50 years, particularly in young people aged 12 to 29 years. As for the Nordic study, they found a higher risk with Spikevax® than with Comirnaty®. This study also confirms the favourable clinical course of myocarditis and pericarditis after vaccination.

- Myocarditis and pericarditis have been added to the list of side effects in the product information of Comirnaty® and Spikevax®, and follow-up is ongoing to identify and understand longer-term outcomes after myocarditis occurring after COVID-19 vaccination in adolescents and adults. In this context, it should be noted that SARS CoV 2 infection is also associated with an increased risk of myocarditis that is exacerbated in young males (336–338).

Guillain-Barré syndrome (GBS)

- Very rare side effect of COVID-19 Vaccine Janssen® and Vaxzevria®
- GBS is a serious nerve inflammation, which may cause temporary loss of feeling and movement (paralysis) and difficulty breathing.

Transverse myelitis

- Transverse myelitis (inflammation in parts of the spinal cord) will be added to the product information as a side effect of COVID-19 Vaccine Janssen®.

Thrombocytopenia and Immune thrombocytopenia (ITP)

- Thrombocytopenia is a common side-effect for Vaxzevria®
 In clinical trials, transient mild thrombocytopenia was commonly reported after vaccination with Vaxzevria®. In post-marketing experience, some severe cases of thrombocytopenia, including cases with bleeding, have been reported.
- Immune-thrombocytopenia (ITP) is as a side-effect of of Vaxzevria® and COVID-19 Vaccine Janssen®
- ITP is a condition in which the immune system mistakenly attacks and destroys blood cells called platelets that are needed for normal blood clotting.

Cerebrovascular venous and sinus thrombosis (CVST)

- Cerebrovascular venous and sinus thrombosis (CVST; blood clots in the brain) without thrombocytopenia has been observed very rarely following vaccination with Vaxzevria®. The majority of these cases occurred within the first four weeks of vaccination. These events may require different treatment approaches than thrombosis with thrombocytopenia syndrome (TTS) and healthcare professionals should consult applicable guidances. CVST will be added to the product information as a side effect of Vaxzevria®.

Venous thromboembolism (VTE)

- Very rare side effect of COVID-19 Vaccine Janssen®. This should be considered for individuals at increased risk for VTE.

Menstrual disorders

- Menstrual disorders after COVID-19 vaccination have also been reported. In Belgium, FAGG/AFMPS has received notifications that include disrupted cycle (prolonged or shortened cycle, breakthrough bleeding), changes in the intensity of bleeding (heavier or lighter periods) and post-menopausal bleeding. No specific clinical pattern is found and the vast majority of these adverse events resolved spontaneously. This signal has also been investigated and discussed by the EMA. To date, no causal relationship can be established. As menstrual changes have been reported after both mRNA and viral-vectored vaccines, if a relationship is established, it is likely to be a result of the immune response to vaccination rather than a specific vaccine component (339). Importantly, there is currently no evidence

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that COVID-19 vaccines cause fertility problems in women or men. More information on the [CDC website](#).

Pregnancy and breast-feeding

Pregnancy and breast feeding are not contraindications to COVID-19 vaccination. In view of increased severity and adverse neonatal outcomes after [SARS-CoV-2 infections in pregnancy](#), Belgium's Superior Health Council has recommended [vaccination with mRNA vaccines of all pregnant women](#) since May 2021, and identified them as [a priority group](#). [recommendations for the use of mRNA vaccines in pregnant women](#). Whilst pregnant women were excluded from the initial vaccination trials, there is now ample evidence of the safety of vaccination in pregnancy. **Two studies from the US, involving over 10,000 women with vaccinations in pregnancy, did NOT show an increase in spontaneous abortions after vaccination** (340,341). These findings are confirmed by another large population-wide study from Scotland, using routine data to follow up 144,548 pregnant women of which 18,399 received COVID-19 vaccination during the pregnancy (342). **Vaccination in pregnancy did NOT lead to increased risk in preterm delivery or perinatal mortality**. Vaccinated pregnant women that were hospitalized with COVID-19 had a 10-fold lower risk to be admitted to intensive care units, compared to unvaccinated women. Moreover, 5,653 SARS-CoV-2 infections in pregnancy lead to 19 perinatal deaths, all in children born from unvaccinated mothers. Indeed, after initial studies showing that vaccine-induced maternal antibodies are transferred through the placenta and breastmilk (343,344), there is now real-world evidence from the US that **maternal vaccination protects also infants <6 months** (345). Data from 379 hospitalized infants showed a maternal vaccine effectiveness of 61% against COVID-hospitalization of the child. The results come mostly from the time period where Delta was dominant, and have been adjusted for age, sex, region and race. Maternal vaccination seems most effective to protect infants when done after 20 weeks of gestation.

Adolescents & Children

Adolescents (12-17y): End of May 2021, Comirnaty's EU authorisation for use was extended to include children aged 12 to 15. End of July 2021, Spikevax's EU authorisation for use was extended 12 to 17 year olds. 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).

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, a phase 1 dose-finding study and an ongoing phase 2-3 randomized trial with 2268 children are being conducted to investigate the safety, immunogenicity, and efficacy of two doses of the BNT162b2 vaccine administered 21 days apart in children 6 months to 11 years of age. Results for the 5-to-11-year-old children have been published. Authors conclude Covid-19 vaccination regimen consisting of two 10-µg doses of BNT162b2 administered 21 days apart was found to be safe and immunogenic with some mild to moderate side effects that improved within a few days and no severe events.

On the 25 November, EMA authorized a paediatric formulation of the Pfizer-BioNTech Comirnaty® vaccine for emergency use in children 5 through 11 years of age and since the 20th December 2021, this is in use in Belgium. It consists of a reduced dose of mRNA (10 µg/dose compared to 30 µg/dose in the adult formulation) and is administered in a two-dose schedule. It is offered to children aged 5-11 years on a voluntary basis and subject to parental (or legal guardian) consent.

Multisystem inflammatory syndrome in children (MIS-C): See for more information section 'Special populations < Children'. MIS-C after COVID-19 vaccination is rare. Based on the national MIS-C surveillance system in the US in over 21 million vaccinated children aged 12-20 years, a reporting rate of 1 case per million children was observed (346). A test negative case-control study among 102 MIS-C patients aged 12-18 years showed an effectiveness of 2 doses of Pfizer-BioNTech vaccine against MIS-C of 91% (95% CI = 78%-97%) (347). Among critically ill MIS-C case-patients requiring life support, all were unvaccinated. Within another cohort of 107 children hospitalized for MIS-C, of which 33 were eligible for vaccination aged 12-18 years, the majority was unvaccinated (26), no one was fully vaccinated and 7 had received 1 vaccine dose (348). The latter had an MIS-C onset after a

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	<p>median of 25 days after their single vaccine dose, suggesting that the SARS-CoV-2 infection occurred before or shortly after vaccination, when immune response was incomplete. These findings suggest that vaccination is effective in preventing MIS-C in persons aged 12–18 years.</p>
<h3>Clinical Aspects</h3>	
<p><u>Modes of transmission</u> <i>Last update</i> 24 February 2022</p>	<p>Evidence indicates that SARS-CoV-2 is transmitted from human to human by infectious droplets (349). 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 (350,351).</p> <p>Transmission may also occur indirectly through contaminated surfaces or fomites, although that risk is generally considered to be low (352). Several studies have shown extensive contamination of inanimate surfaces around an infected person (353) and other respiratory illnesses and coronaviruses can spread through indirect contact (158). 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 (354,355). 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 (352,356). Viral stability and disinfection efficacy may vary somewhat by SARS-CoV-2 variant. A pre-print from Japan reported that on plastic and skin surfaces, Alpha, Beta, Delta, and Omicron variants exhibited more than two-fold longer survival than the Wuhan strain, and the Omicron variant had the longest survival time (357). In vitro, Alpha, Beta, Delta, and Omicron were slightly more resistant to ethanol than the Wuhan strain, but ex vivo evaluation showed that on human skin, all viruses were completely inactivated by ethanol.</p> <p>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 (358–360). Especially in faeces, viral RNA seems to be present later and persists longer than in samples from the upper respiratory tract (361). Faeco-oral transmission therefore was considered but does not seem to be an important route. Presence of viral RNA does not equal infectious potential. A German team analyzed samples from 9 patients and 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 (358,362,363) but no cases of faeco-oral transmission have been documented (356). Finally, although in limited number, PCR-positive conjunctival swabs have been reported in COVID-19 patients, with or without ocular symptoms (eg. conjunctivitis), indicating a potential route of transmission via the ocular mucosa (364). 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).</p> <p>For information on SARS-CoV-2 and blood donations, cfr ECDC document on COVID-19 and supply of substances of human origin.</p> <p>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 (365). 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 (366) and unclear in another (367). In the third study (368), 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 (369,370) and previous experience with SARS (371–373). 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) (374), in fitness centres during Zumba classes (375), during a choir rehearsal (376), in a restaurant without fresh air supply but air being recirculated by the air conditioning (377) or among Chinese bus passengers (378).</p>

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	<p>Reassuringly, all these outbreaks involve <u>prolonged exposure</u> 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 (379).</p> <p>For the potential of intrauterine <u>mother-to-child transmission</u>, see section 'Pregnancy'.</p>
<p><u>Incubation period</u> <i>Last update</i> 24 February 2022</p>	<p>The mean incubation period (the period between infection and onset of symptoms) was for the original strain (Wuhan strain) about 4–6 days with about 95% of individuals developing symptoms within 14 days from infection (380–382). Larger studies and meta-analyses have been carried out, and confirmed a median incubation period ranging between 5 and 6 days (383,384). A systematic review and meta-analysis demonstrated a median incubation period of 5.8 days (95%CI: 5.3-6.2) (385). Another epidemiological interval is the serial interval: the period between onset of symptoms in the primary case and onset of symptoms in the secondary case. A rapid review of 40 studies found a median serial interval ranging from 1.0 to 6.0 days (based on 15 estimates) (386) and a meta-analysis of 11 studies calculated a pooled estimate of 5.4 days (387). Finally, the mean generation interval (the time between 1 person being infected and that person infecting someone else) was estimated through modelling by UHasselt. They used outbreak data from clusters in Singapore and Tianjin, China and found a mean generation interval of 5.20 days for Singapore and 3.95 days for Tianjin (388).</p> <p>With the emergence of the more transmissible Delta variant, it had been hypothesized that the incubation period might have shortened, but there was never sufficient evidence to conclude that this was effectively so. Different analyses (mostly pre-prints) by the same group of authors and of the same outbreak in China reported epidemiological parameters. One analysis estimated the mean incubation period at 5.8 days with 95% of the infected persons developing symptoms within 11.5 days (389). This is in line with previous estimates for the Wuhan strain as noted above. However, in another analysis, <i>Zhang et al.</i> observed a mean incubation period of 4.4 days which seems slightly shorter (390). Regarding the serial interval, while <i>Kang et al.</i> demonstrated a time-varying serial interval which has been reduced to 4.0 days in mid-June 2021 (389), <i>Zhang et al.</i> observed a mean serial interval of 2.3 days for the same outbreak (390). Only one other study, using data from 32 household transmission pairs in Singapore, observed no difference in the serial interval period of Delta vs. wild-type virus (391). Finally, <i>Zhang et al.</i> observed a generation time of 2.9 days (390). In contrast, higher viral load early on in the infection (and hence higher infectiousness soon after exposure) might explain the higher transmissibility (392).</p> <p>There is evidence that the incubation period and serial interval of the Omicron variant are shorter than that of previous variants. In an outbreak in Norway with 81 Omicron infections, the incubation period for symptomatic cases ranged from 0 to 8 days with a median of 3 days (IQR: 3–4), which was shorter compared with previous reports for Delta and other previously circulating variants (4.3 and 5.0 days, respectively) (393). A household cluster investigation in the US found a median incubation period of 73 hours (+/- 3 days) (394). A study in South Korea analysed contact tracing data and estimated the mean serial interval to be 2.2 days (SD +/-1.62)(395). A study in the Netherlands of pairs of a primary case and a secondary case (identified through contact tracing), calculated a mean serial interval of 3.4 days for the 150 SGTF within-household pairs, which was significantly shorter than the mean serial interval of 3.9 days for the 728 non-SGTF within-household pairs.</p>
<p><u>Contagiousness and contagious period</u> <i>Last update</i> 24 February 2022</p>	<p>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 (396–403). 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 (404).</p> <p>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 (374,405–407). In the study in Brunei, household attack rates of symptomatic cases were higher (14.4%) than pre-</p>

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symptomatic cases (6.1%). 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 (408).

Throughout the epidemic, evidence of pre-symptomatic transmission has accumulated (399,405,408–411). 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 (412). 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 (402). 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.

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 (413). 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 (414). 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 (415). 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 (416).

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 were heterogeneous, e.g. with regards to disease severity and immunosuppression. Studies assessing viral culture generally included 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 (417).

Studies on dynamics of viral load, contact tracing and modelling studies were 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 did however describe a positive viral culture in a hospitalized patient (no further details) as long as 32d after symptom onset (418).

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 (419)

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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) was of high quality. In the study, 100 confirmed cases (of which 6 severe) and their 2,761 close contacts were followed up. Only 22 secondary cases occurred. No secondary cases were observed in those exposed to the index case more than 5 days after onset of symptoms (SAR 22/1,818 = 1.0% [0.6%-1.6%] first 5d vs. 0/852 = 0% [0-0.4%]) (405).

The first viral culture data came from a small study of Wölfel et al in 9 patients with mild disease. In these patients, no viable virus was cultured more than 8 days after symptom onset, although viral loads sometimes remained high (420). Since then, the study with the largest sample size that has been published is by Singanayagam et al (421). This group in the UK examined a total of 324 samples from mostly asymptomatic or mild-to-moderate cases (n=233, 92%) and some severe/critical cases. All samples were from the upper respiratory tract but sampled in various ways (nasal, oral, combined, nasopharyngeal swab or nasopharyngeal aspirate). Date of symptom onset was available for 246 samples. Culture-positivity was clearly associated with a shorter time after symptom onset. Despite the various sampling techniques, viral load (as expressed by Ct-values) was both associated with days from symptom onset and with culture positivity. Of note is that the number of samples tested after more than 10 days was low.

Data on the duration of infectiousness of the **Omicron** variant are accumulating and tend to point towards a duration that exceeds 5 days and even 7 days.

A preliminary report of the Japanese National Institute of Infectious Diseases presents the results of an examination of 83 respiratory specimens from 21 cases (19 vaccinees and 2 unvaccinated cases; 4 asymptomatic and 17 mild cases)(422). The amount of viral RNA was highest on 3-6 days after diagnosis or symptom onset, and then gradually decreased over time, with a marked decrease after 10 days. The positive virus isolation results showed a similar trend and no infectious virus in the respiratory samples was detected after 10 days.

In a daily occupational screening program in the US, Omicron infections (N=97) had a mean duration of 9.87 days (95% CI 8.83-10.9) compared to 10.9 days (95% CI 9.41-12.4) for Delta infections (N=107) (423). The peak viral RNA based on Ct values was lower for Omicron infections than for Delta infections and the clearance phase was shorter for Omicron infections, though the rate of clearance was similar. Of 27 Omicron-infected individuals testing positive \leq 1 day after a previous negative or inconclusive test, 52.0% (13/25) were PCR positive with Ct values <30 at day 5, 25.0% (6/24) at day 6, and 13.0% (3/23) on day 7 post detection. Of 70 Omicron-infected individuals detected \geq 2 days after a previous negative or inconclusive test, 39.1% (25/64) were PCR positive with Ct values <30 at day 5, 33.3% (21/63) at day 6, and 22.2% (14/63) on day 7 post detection. Eight days after the first detection, 10-15% still had a Ct value <30 . Only after 10 days this was 0%.

In a study among 260 health care workers in the US who had tested positive for COVID-19 and were allowed to return to work after day 5 if symptoms had improved, 43% (134 of 309) of all RATs were positive between days 5-10 (424). The greatest percent positive RAT was noted on day 6 (58%); on day 8 and 9, 26% had a positive test.

Immunocompromised and severe disease: for a full appraisal of the available evidence on this topic, see the [advice of the Risk Assessment Group](#).

Contagiousness of infections post-vaccination: Initial evidence indicated that persons with an infection post-vaccination had lower viral loads (425,426) and hence might be less infectious (427,428). Data from contact tracing in several countries, including Belgium, confirmed that high-risk contacts of vaccinated index cases were only about half as likely to become infected as high-risk

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	<p>contacts of unvaccinated index cases (429–432). Put differently, breakthrough cases seemed less contagious. Since the introduction of the Delta variant however, studies have shown similar viral loads for vaccinated cases compared to unvaccinated cases (238,433–435). Importantly though, viral load in an infected individual is dynamic, changing over time. Four pre-print studies with longitudinal follow-up of cases have shown a more rapid decline in viral load in vaccinated individuals compared to non-vaccinated (238,436,437). This was also observed in a prospective observational study in the UK, published in the <i>Lancet Infectious Diseases</i> (287). Studies trying to culture live virus from breakthrough cases with the delta variant have shown conflicting results: whilst in a US sample no difference was found (434), a Dutch study found that it was more difficult to culture live virus from vaccinated cases, even when correcting for viral load ($p=0.002$) (436). The US sample attempted culture of 55 samples (of which 39 vaccinated cases) with ct value <25, and could isolate live virus in 37/39 cases. The Dutch study included 222 specimens (of which 70 vaccinated) regardless of ct-value. They concluded that 68.7% of vaccinated cases presented with infectious virus at some point, vs. 84.9% for unvaccinated cases ($p=0.005$).</p> <p>A study in Switzerland assessed quantitative infectious viral titres (IVT) by focus-forming assay in unvaccinated individuals infected with pre-VOC SARS-CoV-2 ($n=118$) or Delta ($n=127$) and vaccine breakthrough infections with Delta ($n=121$) or Omicron ($n=18$) (438). They observed significantly higher IVTs in Delta infected individuals. Vaccinated Delta infected individuals had significantly lower IVTs compared to unvaccinated subjects and cleared virus faster. Vaccinated individuals with Omicron infection had comparable IVTs to Delta breakthrough infections. A study in Qatar found that Ct values in Omicron infections were 0.86 cycles (95% CI: 0.72-1.00) higher for those who received their booster in the preceding month than for unvaccinated persons (50).</p> <p>More information on the protection of vaccination against further transmission is available in the corresponding chapter in the Vaccine Effectiveness section.</p>
<p>Asymptomatic infections Last update 1 March 2022</p>	<p>Asymptomatic infection at the time of laboratory confirmation has been reported from many settings (416,439–444), including pregnant women (445) and nursing home residents (446). The reported proportions of asymptomatic infections have varied widely, from 17.9% (440) to well over 60% (447). These differences are most likely due to incomplete symptom assessment and lack of follow-up (448) 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 (449). Another review, including only 13 studies at low risk of bias, concluded that 17% of cases remain asymptomatic (14-20%) (450). 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 (451) as well as in various other studies (450,452,453). 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 (448,454). Interestingly, an article in <i>Nature Communications</i> describes how all 3 children of two infected parents developed an antibody-response against SARS-CoV-2, although nasopharyngeal PCR swabs were repeatedly negative (455). 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 (397,416).</p> <p>Data from vaccine effectiveness trials in South Africa suggest that Omicron might have a higher rate of asymptomatic carriage than previous variants (456). In one trial, a much larger proportion (31% or 71/230) of the asymptomatic study participants tested positive for SARS-CoV-2 at enrollment in the period that Omicron had become dominant, compared to only 0.6% in the period when the Beta variant was dominant. Half (48%) of these cases had a high viral load ($Ct < 25$). In another trial, 16% of asymptomatic participants tested positive at follow-up during the Omicron wave, while at enrollment, during the period Delta was dominant, this was only 2.4%.</p>
<p>Symptoms Last update</p>	<p>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%</p>

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<p>1 March 2022</p>	<p>initially presented with fever (although 89% developed fever at some point during hospitalization) and 68% with cough (382). Other symptoms included fatigue (23%), myalgia (15%), and gastrointestinal symptoms (+8%) (457). 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 (458).</p> <p>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 urticaria) (459–462). Chemosensory dysfunction, such as anosmia and dysgeusia (either isolated or in combination with other symptoms) were 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 (463,464). Notably, anosmia has been reported after infection with other respiratory or coronaviruses (465). 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) (466).</p> <p>Data from more than 72,000 cases from China classified cases as mild (81%), severe (14%), or critical (5%) (467). 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).</p> <p>The broad spectrum of atypical COVID-19 symptoms complicates the differential diagnosis with other respiratory infections. The best predictor of a COVID-19 infection were the olfactory and/or gustatory dysfunctions (468). Other symptoms that appear more frequent in COVID-19 in comparison to other respiratory infections are fever, myalgia and general malaise/fatigue (469–472). None of these symptoms is however specific enough to be used in a presumptive differential diagnosis.</p> <p>The clinical spectrum of Omicron appears to be slightly different from that of previous variants. An analysis in the UK compared the symptoms of Omicron cases, reported to NHS Test and Trace, with those of Delta cases during the period when both variants were circulating (51). After adjusting for age, sex, vaccination status, and other possible confounders, sore throat was more likely to be reported by cases with Omicron (AOR 1.93, 95% CI: 1.88-1.98) and loss of smell and taste less common (AOR 0.22, 95% CI: 0.21-0.23). The same was observed in a study by Oxford University that also found that sore throat became more commonly reported in symptomatic PCR-negative cases, suggesting that sore throat may not be a specific predictor of SARS-CoV-2 infection with Omicron.</p>
<p><u>Complications and mortality</u> Last update 9 October 2020</p>	<p>As aforementioned, according to the Chinese experience, severe cases and critical cases occurred, during the period that the original Wuhan strain was dominant, in approximately 14% and 5% respectively. These cases presented 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, presented 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.) (473,474). For the severity of COVID-19 caused by the Omiron variant, see the section Genetic diversity & viral variants.</p> <p>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</p>

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	<p>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 (475), only few case reports are found in the scientific literature (476,477) 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.</p> <p>Evidence is emerging that COVID-19 is associated with an increased risk of thromboembolic disease (478,479) and a high rate of cardiovascular complications (462). 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) (480). In a double-center study in the Netherlands, a 31% incidence of thrombotic complications in ICU patients with COVID-19 infections is reported (481).</p> <p>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% (142). In Wuhan, in admitted patients, mortality reached 25% in the middle of the epidemic (457). On March 22, the CFR in the oldest age group (>80y) in Italy was 23% (482). 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% (483). 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 (484). 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. (485) The overall infection fatality risk was 1.1-1.4% in men and 0.6-0.8% in women, which is higher than for e.g. Influenza. There was a marked difference by age and sex, ranging from 0.01% in girls 0-9y old to 16.4% in men aged 80 years and older.</p> <p>For Belgium, mortality is reported within the daily and weekly epidemiological reports link.</p> <p>In children, reports of a Kawasaki-like disease are increasingly reported, see section epidemiology > children.</p>
<p>Long COVID Last update 08 March 2022</p>	<p>Although a consensus definition is lacking, post-COVID conditions are generally defined as persistent or new onset symptoms or delayed or long-term complications beyond 4 weeks from the onset of symptoms (486,487). WHO formulated the case definition as ‘a condition that occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis’ (488). 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 (489).</p> <p>The pathophysiology is not yet fully understood and consists probably of multiple, intertwined mechanisms (490,491). Two categories of mechanisms are distinguished (489,491): (i) direct organ damage or endothelial dysfunction caused by the virus and (ii) persisting inflammation, thrombosis and autoimmunity.</p> <p>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 (489,491–493). Post-COVID conditions not only appear in patients that have been severely ill but even in patients that remained asymptomatic (487). 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 (494). The COVID Symptoms Study from King’s</p>

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College London found that long COVID was more likely with increasing age and body mass index and in females (493,495). 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 (496). For more information on long-COVID in children, see section [children](#).

Many different organs are affected, in particular heart, lungs and brain (489). 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. (489,491,495,497,498). 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 (499–504). 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) (505–508). 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 (509). 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 (490,491).

Post-COVID symptoms can have an **impact on the person's functioning**. In a study in the UK, 64% of individuals with post-COVID reported that they could not function normally, 32% that they could not function without assistance, 17% that they could not work, and 66% had taken sick leave (510). ECDC therefore expects post-COVID to create a high burden, with additional pressures on the health care system (511).

There is no simple test for **diagnosing** long COVID (489). 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 (512).

Further studies are necessary to know how to **follow-up** COVID-19 patients but also to prevent these long-term consequences (513). A multidisciplinary, multispecialty approach will most probably be required (489,514). The [Belgian Health Care Knowledge Centre](#) (KCE) conducted a study on the needs and follow-up of people with long COVID. A short report can be found on the [website of the KCE](#).

There remain many uncertainties about long COVID in children. In general, **persisting symptoms seem less frequent in children than in adults** (515–517). A UK survey among 434 secondary school students with a positive test, showed that 1 out of 8 (12.3% [8.5-16.9%]) still reported symptoms more than 4 weeks after the infection (517). The most frequently reported symptom was fatigue. For 9.4% of those with ongoing symptoms, it was difficult to carry on with their activities of daily life. The exact prevalence of persisting symptoms differs however amongst studies. Other prospectively collected UK data from 75,529 children and adolescents with a positive test show that only 4.4% still had symptoms after >4 weeks (as reported by an adult proxy) (518). Prevalence was correlated with higher age. Moreover, as cross-sectional surveys have shown a high prevalence of symptoms like fatigue and headache even among children and adolescents tested negative for SARS-CoV-2 (516,518–520), it is important to also include a control group. Several studies have indeed shown a significantly higher proportion of persisting symptoms after a positive test, when compared to persons with a negative SARS-CoV-2 (516,518–520). However, in 1 study, the difference was only significant for “loss of taste and smell”, which lingered on in 16.6% of secondary school and 5.0% of primary school pupils, compared to only 0.4% of those with a negative test (520). Finally, while most studies find higher proportions of persisting symptoms in older age groups (515,516,519), a study from Norway suggests the highest prevalence is in the age group 1-5 years (521). Using national reimbursement data, the authors compared healthcare use between people aged 1-17y, of which

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10,279 tested positive and 275,859 tested negative. In general, there was very limited use of healthcare after

Immunopathogenesis

Pathogenesis

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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 (522). 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 (522).

Persistence of **high viral loads** has been associated with disease severity (523). 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 (524). The 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 (525). 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 TNF α were significantly higher in intensive care unit (ICU) patients than non-ICU patients (526). 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 (527). 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) (525).

Post-mortem autopsies of 3 patients have revealed the presence of viral elements within endothelial cells and an accumulation of inflammatory cells, with evidence of endothelial and inflammatory cell death. SARS-CoV-2 infection may therefore induce endotheliitis in several organs as a direct consequence of viral involvement and of the host inflammatory response, potentially explaining the systemic impaired microcirculatory function found in different vascular beds of patients with COVID-19 (528).

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 (457,473,529,530). In-hospital death has been associated with d-dimer concentrations greater than 1 $\mu\text{g/mL}$ (odds ratio 18.42, 95%CI 2.64-128.55; $p=0.0033$) on admission (457). 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 (530). 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.

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	<p>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 (531).</p> <p>An additional mechanism of disease pathogenesis hypothesized by several authors is antibody-dependent enhancement (ADE) (532,533). 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 (534). Whether ADE is involved or not in SARS-CoV-2 disease pathogenesis is still unknown.</p> <p>Several laboratory studies have shown that the Omicron variant multiplies much faster in the bronchus as previous variants did, but does not infect cells deep in the lung as readily, which explains its lower disease severity (535,536).</p>
<p>Immunity Last update 17 March 2022</p>	<p>Humoral response: The majority of COVID-confirmed patients develop SARS-CoV-2 specific antibodies (IgM, IgA and IgG) against the viral S and N protein within 1-3 weeks after symptom onset, that remain elevated after initial viral clearance. The kinetics of SARS-CoV-2 specific antibodies are developed in section on 'Serology' below.</p> <p>Notably, the level of the antibody response mounted after infection shows a positive correlation with the degree of disease severity (537–540). Longitudinal follow-up of COVID-19 patients has shown that antibody levels may rapidly wane, declining within 2 months after symptom onset (538,539) but thereafter remain relatively stable for 6-12 months (541–543). Type of assay used and methodological design may explain dissimilarities between studies. As Seow <i>et al</i> showed, if in a majority of individuals IgM and IgA rapidly declined, IgG levels remained high during the 94 day study period, but differences were seen with regards to their neutralizing potential (see nAbs below) (537). Several studies have shown that vaccination of seropositive individuals importantly increases all components of the humoral response, including cross-protective neutralizing antibodies against SARS-CoV-2 variants (541,543,544).</p> <p>Virus-specific neutralizing antibodies (nAbs) are antibodies that not only bind to a virus, but also block viral infection of the host cell. Highly effective nAbs protect against future infections and are currently considered as the best available indicator of protection against reinfection. In SARS-CoV-2, the S protein epitopes, including RBD epitopes, are the main targets of nAbs (545,546).</p> <p>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 (547). In this study and others, the magnitude of the nAb response, as for total antibody levels, correlated with disease severity (537,547). In the above mentioned longitudinal study by Seow <i>et al</i>, assessing the kinetics of nAbs in 65 PCR-confirmed COVID-19 cases, nAb titers peaked on average at day 23 post-onset of symptoms, and then decreased 2- to 23-fold during the 18-65 days follow up. In individuals that had developed only modest nAb titers following infection, nAbs became undetectable or approached baseline after +/- 50 days. In contrast, those with high peaks of nAb titers maintained these level for >60days (537).</p> <p>nAbs titers are often measured to determine protection against infection and cross-protection against infection with different variants. As the main target of nAbs is the S-protein, which carries variant-specific mutations, nAb responses have shown variable efficacy against different variants. Several studies have shown, for instance, that sera from convalescent patients (infected with the Alpha, Beta</p>

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	<p>or Delta variant) largely did not neutralize the Omicron variant, although cross-neutralization was observed against other variants (242).</p> <p>Cellular response: Various studies have shown that virus-specific T cell responses can be detected in convalescent COVID-19 patients (548–557), even in seronegative patients indicating that immunity can be maintained even in the absence of circulating antibodies (548,552,553,558). SARS-CoV-2 specific T-cell responses are significantly associated with milder disease, suggesting that T-cell responses maybe important for control and resolution of a primary SARS-CoV-2 infection (548,549,551,559).</p> <p>Looking at the T-cell subsets, CD4+ responses were established in >90 % of convalescent patients and CD8+ responses in 70% of the cases (555).</p> <p>Using different SARS-CoV-2 epitopes, it was shown that the strongest T-cells responses were against the spike protein (554,555), but also responses against membrane, nucleocapsid, env and ORFs were observed (548–550,553–555). Although not observed in all studies (549,560), it is interesting that in several studies T cell reactivity to SARS-CoV-2 epitopes was detected in 20-60% of healthy individuals (548,550,554–556), which is indicative of the presence of cross-reactivity due to previous infection with ‘common cold’ coronaviruses. Several studies analysed the cellular immune response to the Omicron variant and showed a high degree of preservation of T cell epitopes between the ancestral strain and Omicron. Keeton et al assessed the ability of T cells to react to the spike protein of Omicron in people who were vaccinated or convalescent. Between 70 % and 80 % of the CD4+ and CD8+ T cell responses to spike was maintained across study groups. The majority of T cell responses induced by vaccination or previous infection cross-recognized variants, suggesting a possible protection against severe disease with Omicron, even when levels of neutralizing antibodies were insufficient to prevent infection (561–563).</p> <p>Immune memory: 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 (564). 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.</p> <p>In case of SARS-CoV-2 infections, memory T cells were shown to exist 6-7 months after infection (565). 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 (553,554,565,566). In a study from Dan et al. 51 subjects provided longitudinal blood samples up to 6 to 8 onths after COVID-19. 95 % of subjects retained immune memory at 6 months after infection. Of note antibody titers were not predictive of memory T cell suggesting that antibody serodiagnostic is not a robust indicator of protective immunity (567).</p> <p>Memory B-cells also accumulate over the first months after SARS-COV-2 infection allowing for new antibodies production upon reinfection (568). Antibodies expressed by memory B-cell have somatic hypermutations leading to potentially increased potency (569).</p> <p>Correlates of immune protection: The contribution of different aspects of immune response and immune memory to the protection against SARS CoV-2 reinfection remains unclear (568). Although antibodies are usually a reasonable correlate of antiviral immunity, and although studies suggest that neutralising antibodies are good correlates of vaccine induced immunity (570,571), 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).</p> <p>Population immunity: The results of population-based sero-epidemiological studies in the general population and in blood donors of the EU/EEA Member States are available at https://www.ecdc.europa.eu/en/covid-19/latest-evidence/immune-responses.</p>
<p>Re-positivity and reinfection Last update 1 April 2022</p>	<p>True reinfection needs to be distinguished from re-positivity (i.e. individuals tested positive for SARS-CoV-2 more than once). Re-positivity can be due to prolonged shedding of non-infectious viral RNA, which is common during SARS-CoV-2 infections, viral reactivation or true reinfection. A previous infection offers some protection against reinfection, but this protection wanes over time and reinfection is certainly possible.</p>

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Definition of reinfection: Confirmed reinfection is usually established on the basis of comparative whole genome sequencing, and the identification of single nucleotides 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 (572,573). When the viruses from two episodes are associated to different clades or lineages, the evidence of reinfection is stronger (574–576).

When genomic sequencing is not possible, reinfections are usually defined based on the period since prior infection. The period elapsed since the previous infection to consider an infection to be a presumed reinfection varies. Before a period of 90 days was generally used, but more and more agency and countries apply a shorter period. In Belgium the period was in April 2022 shortened from 90 days to 60 days, following ECDC recommendations (577).

Frequency of presumed reinfections and prior infection effectiveness: A large multi-centre prospective cohort study in the **pre-Omicron** era 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 (defined as a positive PCR test \geq 90 days), corresponding with 3.3 reinfections/100,000 person-days (578). Compared to a control group of 14,173 'naïve' HCW, the risk of infection was significantly lower in those with previous infection: OR for reinfection of 0.17. Likewise, an adjusted hazard ratio of 0.11, or a reduction of the risk with almost 90%, was found in another prospective study in the UK among 1265 HCW with positive serology and 11,364 seronegative health care workers (579). In those studies from the UK, reinfection occurred in 0.67% and 0.16% of cases. Several other studies, both prospectively following cohorts of healthy adults (542,580,581) or retrospective designs using population-wide data (582–585), have confirmed that infections in previously positive individuals are 80-95% less frequent than in naïve individuals in the 6-12 months after initial infection. Importantly, these studies did not assess the impact of SARS-CoV-2 variants with possible immune escape. 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 (586) (see also section [genetic diversity and variants](#)).

Immunity from infections by previous variants is less effective against reinfection with the **Omicron** variant. A study from the UK found that the neutralizing response in unvaccinated individuals previously infected with Delta was 29 times less potent against Omicron than against Delta (587). In fully-vaccinated individuals the reduction was, however, less outspoken (4.5 times less). Epidemiological data from South Africa and England showed a relatively much higher level of reinfections during the current Omicron wave than during previous waves (244). In England, the population of previous infections eligible to become a reinfection were used as a denominator, to control for the increase in people ever infected (34). In the Netherlands, a multivariate analysis found an increased risk of Omicron infection vs. Delta infection in previously infected individuals compared with infected naïve individuals (OR=4.9; 95%CI 3.1-7.7) (588). A test-negative case-control study in Qatar estimated the 'prior infection effectiveness' against symptomatic reinfection with Omicron to be 56.0% (95% CI: 50.6-60.9), compared to 90.2% (95% CI: 60.2-97.6) against Alpha, 84.8% (95% CI: 74.5-91.0) against Beta and 92.0% (95% CI: 87.9-94.7) against Delta (589). Protection against hospitalization or death after an Omicron infection was not statistically different from that for previous variants: 87.8% (95% CI: 47.5-97.1) for Omicron, 69.4% (95% CI: -143.6-96.2) for Alpha, 88.0% (95% CI: 50.7-97.1) for Beta and 100% (95% CI: 43.3-99.8) for Delta. Immunity from an Omicron infection, however, might be more effective in preventing a new Omicron infection. A South African in-vitro study found that neutralization of Omicron, elicited by an Omicron infection, increased 14-fold during the 14 days period after enrollment (590). Interestingly, also the neutralization of Delta increased 4.4 fold.

The extent of cross-immunity between the BA.1 and **BA.2** Omicron sublineages is still uncertain. While in the UK no BA.2 infections have yet been identified in individuals previously infected with BA.1, a study in Denmark identified 47 of such reinfections, relatively short after the primary infection (591). Most of these were in unvaccinated young individuals causing mild disease. A matched retrospective cohort study in Qatar estimated the effectiveness of BA.1 infection against

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reinfection with BA.2, 15 days after the start of follow-up, at 94.9% (95% CI: 88.4-97.8%), and of BA.2 infection against reinfection with BA.1 at 85.6% (95% CI: 77.4-90.9%) (592).

Frequency of confirmed reinfections: Studies investigating the frequency of confirmed reinfections are scarce. Since the appearance of the Omicron variant, some countries have documented reinfections with another variant in relatively short periods after infection with a previous variant. In the UK, 31 cases of a total of 186,896 BA.1-confirmed cases identified by genome sequencing had a sequencing sample with an interval of 20 to 72 days after the previous positive test (593). Thirty of these were BA.2 and one was Delta. In Denmark, of 1,848,466 positive cases 1,739 were in the same person in a time of 20 to 60 days. Of 263 of these individuals, the two samples were sequenced (594). 50 individuals (19%) had the same variant in the second sample (and thus possibly the same infection) and 187 (71%) a different variant (and therefore definitely a reinfection). Of the latter, 140 were a BA.2 re-infection after a Delta infection and 47 a BA.2 re-infection after a BA.1 infection. Data from Qatar show that re-infections with a different subtype can occur within an interval of less than 14 days (592). In a retrospective cohort of approximately 20,000 BA.1 infections there were 17 documented new positive PCR tests in a median follow-up period of 14 days (IQR 12-17) and of which 10 were sequenced and one was a BA.2 infection. In a cohort of approximately 100,000 BA.2 infections, there were 160 new positive PCR tests in a median follow-up period of 12 days (8-15), of which 44 were sequenced and 11 were BA.1 infections.

Underlying causes: 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 reinfected patient was analysed (595). 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) (596). Follow-up of antibody responses during 13 months after infection in 393 health-care workers did not show any effect of BMI or age, but showed faster decay in anti-RBD IgG in men than in women (541). In contrast, a large population-wide study in Denmark showed markedly higher levels of reinfection in those older than 65y than in the younger age groups (582). Higher IgG levels have been associated with severe disease, but even mild disease seems to offer good protection for at least 6-8 months (541,542,581).

Infectiousness of reinfections: Initially, data on the potential of virus transmission from re-infected cases was scarce, but later data indicated that, during the period that the Alpha variant was dominant, reinfections had on average a significant lower, but still infectious, viral load than primary infections. A case series of 7 reinfection cases, reported low viral loads and asymptomatic infections in 6 out of 7 cases of reinfection. The 7th case, a symptomatic reinfection with high viral loads within 25 days after initial infection was found to be mildly immunosuppressed (580). A more extensive analysis in Qatar, comprising 1695 reinfections in unvaccinated individuals, found that, after adjusting for sex, age, nationality, reason for testing, and calendar week, the Ct value was on average 3.7 (95% CI: 3.4-4.0) cycles higher compared to primary infections in unvaccinated individuals (597). A more recent analysis in Qatar, assessing Omicron infections in 141,839 individuals without and 13,803 with previous COVID-19 infection, found that the Ct value was 1.30 (95% CI: 1.20-1.39) cycles higher for those with a prior infection compared to those without prior infection, signifying lower infectiousness (50).

Prolonged viral shedding and re-positivity: 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 (598). One study even described a positive PCR result 104 days after the first positive test in an obstetric patient (599). 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 (600). 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 (600-602), but there is no established link between a weaker immunity in

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	<p>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) (603). 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 (603). In practice, a repeat positive SARS-CoV-2 PCR test less than 60 days after a previous positive PCR test is now generally considered to be probably prolonged viral shedding and no re-infection.</p> <p>Prolonged viral shedding-associated re-positive cases are thought to be non-contagious. The Korean CDC published a report on the epidemiological and contact-investigation of 285 re-positive cases. Re-positive cases were detected either through screening (59.6%) or because of symptoms (44,7%). Time from initial symptom onset and re-positivity sampling ranged from 8 to 82 days (average 44.9days). Additional virological testing was performed for 108 of these re-positive cases: low viral loads were found in a majority of cases (89.5% had Ct values >30) and viral cell culture was negative for all. For these re-positive cases, 790 contacts were identified, among which only 3 newly-confirmed cases were identified. These 3 cases had additional high-risk exposures to COVID-19 to the exposure to the re-positive case. Overall, no evidence indicating infectivity of re-positive cases was found (604). Similarly, follow-up of 203 individuals infected with the Wuhan strain revealed that 5% still presented positive PCR-results on pharyngeal swab 90 days after initial infection, but no transmission to close contacts was observed after the post-symptomatic stage (605).</p>
<h3>Diagnosis and testing</h3>	
<p>Introduction Last update 1 March 2022</p>	<p>COVID-19 is confirmed by either the identification of the SARS-CoV-2 RNA in biological samples through nucleic acid amplification, or the detection of SARS-CoV-2 antigen using immunoassays.</p> <p>In addition, clinical presentation (cfr. Clinical aspects), biological markers, and imagery contribute to the diagnosis of COVID-19.</p> <p>There is no perfect ‘gold standard test’ for the diagnosis of COVID-19 to which diagnostic tools can be compared to. Reported sensitivities and specificities should be considered with caution. Moreover, the positive and negative predictive values of the test will depend on the prevalence of the virus and therefore on the test indication (for example screening vs. diagnosis) and 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.</p>
<p>Laboratory findings Last update 8 December 2020</p>	<p>In a retrospective cohort study including 191 PCR-confirmed adult inpatients (Wuhan, China), 40% had lymphopenia ($< 0.8 \times 10^9/L$), 67% had elevated Lactate dehydrogenase (LDH $> 245 U/L$), and 80% had $>300 \mu g/L$ of serum ferritin on hospital admission (457). A systematic review and meta-analysis conducted in April 2020, observed that the most prevalent laboratory findings 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 (606).</p>
<p>Nucleic acid amplification tests (NAATs) Last update 3 March 2022</p>	<p>RT-PCR</p> <p>The majority of molecular diagnostics developed for the detection of SARS-CoV-2 involve reverse transcriptase polymerase chain reaction (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</p>

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	<p>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.</p> <p>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. 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.</p> <ul style="list-style-type: none"> • Timing of testing: In a literature review and pooled analysis, Kucirka <i>et al</i> 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 (607). 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 (608). • 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 (609,610), and assays have used different primers and probes. Instructions for test validation in Belgium are available in Fr and Nl. <p>Specificity of RT-PCR for the diagnosis of COVID-19 is high (in the order of >99.5%) (611). With the exception of SARS-CoV, no cross-reactivity is found when tested against a large panel of microorganisms including the common human coronaviruses (612). 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.</p>
	<p>Other Nucleic Acid Amplification Tests</p> <p>There are a number of nucleic acid amplification tests 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 (613,614). Their specificity is similar to that of an RT-PCR, but their sensitivity is slightly lower (615).</p>
	<p>Rapid NAATs</p> <p>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’. Other platforms, such as the Cobas Liat test of Roche, provide results even faster (+/- 20 minutes) and can be used at the point-of-care. Their performance in terms of sensitivity and specificity is similar to that of the standard RT-PCR tests (616–619), but their cost is higher. There also exist rapid PoC tests using isothermal NAAT, such as the Abbott ID NOW test, but with a lower sensitivity than the rapid RT-PCR tests (615,620).</p>

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<p>Sample type Last update 02 February 2022</p>	<p>Respiratory samples</p> <p>Sensitivity of RT-PCR appears to be higher for lower respiratory samples than for upper respiratory tract samples (358,396,621). 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 (397–400). RT-PCR may remain positive longer in lower respiratory samples (396,621). In a prospective cohort of 67 COVID-19 pneumonia cases (Chongqing, China), median duration of SARS-CoV-2 RNA shedding was 12 days (3-38 days) in nasopharyngeal swab versus 19 days (5-37 days) in sputum. In this study, prolonged viral shedding was also observed in severe patients compared to non-severe patients (621).</p> <p>Nasopharyngeal swabs (NPS) can cause discomfort and alternative respiratory samples have therefore been proposed. Nasal swabs are easier to collect and commonly used for self-swabbing and self-testing. The swab can either be collected mid-turbinate or in the anterior nasal area. This comes, however, at the cost of a loss of sensitivity. A systematic review examining the performance of any additional respiratory specimens to NPS found that pooled nasal and throat swabs gave the highest sensitivity compared to NPS (97%), whereas lower sensitivities were achieved by nasal swabs (86%) and a much lower sensitivity by throat swabs (68%) (622).</p> <p>Concerns have been raised if the above findings can be extrapolated to the Omicron variant. A study in South Africa compared RT-PCR on mid-turbinate nasal swabs with RT-PCR on saliva swabs among 382 symptomatic patients and found a sensitivity for detecting the Omicron variant, using being positive on either sample as reference, of 100% (95% CI: 90-100%) for the saliva swabs and 86% (95% CI: 71-94%) for the mid-turbinate swabs. (623). For the Delta variant the sensitivity was higher on the mid-turbinate swabs (100%; 95% CI: 89-100%) than on the saliva swabs (71%; 95% CI: 53-84%). The lower sensitivity of rapid Ag tests on self-collected nasal swabs, compared to RT-PCR on saliva, in the early phase of infection, that was encountered in the clinical study in the US mentioned below in the section on rapid Ag tests (624), could also be attributed to a later presentation of the virus in the nasal area. The NRC has compared the PCR result and viral load (Cq) among 264 patients sampled twice, once nasopharyngeal and once oropharyngeal (625). 80 patients tested positive, among which 88.8% (71) tested positive on both swabs, 7.5% (6) tested positive only on the oropharyngeal swab and 3.8% (3) patients tested positive only on the nasopharyngeal swab. There are thus some indications that, contrary to earlier variants, Omicron might present earlier in the throat than in the nasal area. However, this needs to be confirmed by more extensive research.</p>
	<p>Oral fluid samples</p> <p>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. 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.</p> <p>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 (622,626–632). 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 have a role in the detection of SARS-CoV-2. Sensitivity is overall similar to NPS in patients with a high viral load (Ct value≤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. 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) (633). In the same study, it was</p>

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	<p>suggested that the detection sensitivity was much better for saliva collection in a container compared to a saliva swab.</p> <p>Sensitivity of saliva specimens varies according to the time of the day. 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, $p < 0.001$) (634). 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 (635). 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 (637). 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 throat, a higher sensitivity than NPS (Defêche 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 (638).</p> <p>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) (639). However, the difference was less in samples with a Ct value ≤ 25 (93.3% and 100%, respectively).</p> <p>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. Studies that included both symptomatic and asymptomatic people consistently found a lower sensitivity in asymptomatic than in symptomatic persons (640–642). 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 (643). 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 $\geq 10^4$ copies/sample, sensitivity was 100% and equal to the sensitivity of the rapid Ag test on NPS.</p> <p>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).</p> <p>For the use of oral fluids for rapid antigen testing see further below.</p>
<p>Impact on other respiratory viruses and multiplex PCR Last update 03 March 2022</p>	<p>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.</p> <p>The measures implemented to contain the spread of the COVID-19 epidemic had clearly also an impact on seasonal epidemics by other respiratory pathogens. 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 (644). 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 (645) and some studies documented lower SARS-CoV-2 positivity rates among flu positive cases than among flu negative cases (646,647). Reduction in the circulation of other seasonal</p>

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	<p>respiratory viruses was observed in the Southern hemisphere during the first peak of the epidemic (648–650) and in the Northern hemisphere during the 2020–2021 flu season (651–653).</p> <p>As a result, co-infections of SARS-CoV-2 and other respiratory viruses are rare. In most studies coinfection was found in only 1% to 2% of the samples (654,655). Some studies observed more extended cases of co-infections with bacterial pathogens (656). However, while coinfections with influenza are rare, coinfecting COVID-19 patients had in one study a 2.27 times greater risk of death than non-co-infected patients (646). 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.</p>
<p>Antigen tests <i>Last update</i> 02 February 2022</p>	<p>Tests detecting antigen in respiratory samples are cheaper and faster than NAATs, and have therefore been developed for the detection of SARS-CoV-2. These tests are most commonly rapid diagnostic tests for use at the PoC, although that they also exist for automated use at laboratories.</p> <p>Rapid antigen tests: These tests are immune-chromatographic assays, and involve the detection of SARS-CoV-2 antigen in respiratory samples. Most tests show overall sensitivities of around 70% (657,658). Sensitivity is generally much better when viral load (Ct<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 (659). Three systematic reviews and meta-analyses have been published to date. The largest of these included 121 evaluations and found an average overall sensitivity of 71.2% (95%CI 68.2%-74.0%), an average sensitivity of 95.8% (95%CI 92.3%-97.8%) in specimens with high viral load (Ct<=25) and an average specificity of 98.9% (95%CI 98.6%-99.1%)(660).</p> <p>The use of rapid antigen tests is therefore mainly considered in patients with recent onset of symptoms (<=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.</p> <p>Performance varies, however, substantially between tests and some rapid Ag tests available on the Belgian market perform rather badly (661). In an evaluation of 64 test kits in the UK, only 19 test kits passed the first evaluation round, and eight of these the second round (658). In Germany, 96 of the 122 evaluated tests met the sensitivity limit of 75% with Ct<=25 (662).</p> <p>All of the above applies to rapid Ag tests performed on nasopharyngeal swabs. The performance of rapid Ag tests on oral fluid samples has been evaluated by several studies (663–669) and some showed very disappointing results with regard to the sensitivity of rapid Ag tests on saliva (665,667–669). Rapid Ag tests on saliva are therefore currently discouraged. The reason for the sometimes much lower sensitivity compared to a rapid Ag test on a NPS is not clear. One author hypothesized that the presence of mucosal secretory immunoglobulins targeting SARS-CoV-2 antigens might compete with the rapid Ag test for the same target (667).</p> <p>An in-vitro analytic study in Switzerland evaluated 7 rapid Ag tests using cultured SARS-CoV-2 Omicron variant, and found that the analytical sensitivity to detect Omicron was lower than for the other variants in most tests evaluated (670). The same authors evaluated retrospectively the sensitivity of five rapid Ag tests on 10 nasopharyngeal specimens that had tested positive for Omicron with RT-PCR (671). With exception of one test, all tests had failures in detecting infections with high viral load or positive on culture. Also a clinical study of an Omicron outbreak in the US found that rapid Ag tests on self-collected nasal swabs, in people who tested positive with RT-PCR on saliva, were mostly negative in the first 3 days after infection, including in several cases where the viral load was already high (624). On the other hand, other in-vitro analytic studies did not find substantial differences in sensitivity for the detection of Omicron compared to Delta ((672–675) and several countries conducted laboratory evaluations of rapid Ag tests and reported a comparable sensitivity to that observed for previous strains (676–678). In addition, in a clinical study in San Francisco 296 nasal samples that had tested positive with RT-PCR for Omicron were retested with a</p>

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	<p>rapid Ag test and the sensitivity was similar to that observed for prior variants (95.2% (95% CI 92-98%); 82.1% (95% CI 77-87%) and 65.2% (95% CI 60-70%) for Ct thresholds of < 30, < 35 and no threshold, respectively) (679). Similar results were obtained in other clinical studies in the US and Spain (680,681). In conclusion, there is currently not enough evidence that rapid Ag tests perform less well in the detection of Omicron compared to previous variants.</p> <p>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, although somewhat better, to that of rapid antigen tests (682,683).</p>
<p><u>Repetitive testing</u> Last update 5 February 2021</p>	<p>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 (684–686). Most studies recommend a periodicity of at least 2-3 times a week (687–690), but others state that relatively infrequent testing, such as every one or two weeks, is already sufficient to keep controlled outbreaks small (691). 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 (692). Models also show that the health benefits of repeated testing with a rapid antigen test far exceed their costs (693).</p> <p>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.</p> <p>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 (694,695). 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 (696).</p>
<p><u>Serology</u> Last update 13 July 2021</p>	<p>Immunological assays, or serology tests, have been developed for the measurement of antibodies directed against SARS-CoV-2 proteins. Currently available assays target antibodies directed against the main immunogenic coronavirus proteins: the N-protein, the S-protein or the Receptor Binding Domain of the S-protein (RBD). For information on use of serology as correlate of protection, see section immunity.</p> <p>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) (697) indicated that:</p> <ul style="list-style-type: none"> - Seroconversion rates are high, with SARS-CoV-2-specific IgG antibodies detected in over 90% of individuals at two weeks and 100% at four weeks. - Immunoglobulin M (IgM) is typically the first antibody to rise in acute infection, followed by immunoglobulin G (IgG) with IgG tending to persist much longer in the body. - The median time to antibody detection following symptom onset ranges from 5 to 17 days for IgM and 6 to 14 days for IgG. - The persistence of antibodies after COVID-19 is still unclear. As mentioned above (cfr section “Immunity”), several studies showed that anti-SARS-CoV-2 antibodies wane overtime while others found antibody persistence for at least 120 days.

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- Correlation between antibody levels and protection against reinfection or disease is currently unclear (540,698)

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 (699).

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) (700). 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 %)(701). An evaluation of COVID 19 serological assays found sensitivities ranging from 81 to 99 % and specificities ranging from 94 to 99 % (700).

Cross-reactivity between seasonal human coronaviruses and the pandemic SARS-CoV-2 needs to be carefully considered in the development and interpretation of assays for precise detection of SARS-CoV-2- specific antibodies. Guo et al found strong cross reactivity of their serological assay with SARS-CoV. In contrast, no cross-reactivity was found with the other human coronaviruses (NL63, 229E, OC43, HKU1). In addition, no anti-SARS-CoV-2 IgM, IgA, or IgG antibodies were detected in 185 control samples (samples from healthy individuals and patients with acute lower respiratory tract infections) (702). Inversely, cross-reactivity has been found when sera from SARS-CoV-2 patients are tested using SARS-CoV serological assays (703). 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 (704) published recommendations in which potential indications for serologic testing are including: 1) evaluation of patients with a high clinical suspicion for COVID-19 when molecular diagnostic testing is negative and at least two weeks have passed since symptom onset; 2) assessment of multisystem inflammatory syndrome in children; and 3) for conducting serosurveillance studies.

In a population where vaccines based on the spike protein are used, serological tests can identify the proportion of vaccinated (anti-spike antibodies only) and infected individuals (presence of anti-nucleocapsid and spike antibodies) (705).

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

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	<p>and the UK is available at https://www.ecdc.europa.eu/en/covid-19/latest-evidence/immune-responses.</p> <p>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 (706).</p>
	<p>Rapid serologic 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% (707). 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%) (708). 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.</p>
<p><u>Waste water surveillance</u> <i>Last update</i> 17 March 2022</p>	<p>An interesting method to early detect SARS-CoV-2 presence is through regular monitoring of wastewater 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 wastewater could be advantageously exploited as an early warning of outbreaks (709,710). An expert consultation organized by WHO in November 2020 concluded that, although that it is not a replacement for existing COVID-19 testing approaches and strategies, surveillance of SARS-CoV-2 in wastewater can provide important complementary and independent information to public health authorities (711). It is a tool to observe trends and not an absolute means to draw conclusions about the prevalence of COVID-19 in the population. More specifically, wastewater surveillance can be used for preventive or early warning purposes, as virus detection in wastewater should be taken as a signal of the possible (re-)emergence of the pandemic. Also the European Commission provided guidance on the use of wastewater surveillance and states that waste water monitoring needs to be systematically included in the national testing strategies for the detection of the SARS-CoV-2 virus (712–714).</p>
<p><u>Chest CT</u> <i>Last update</i> 19 April 2020</p>	<p>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 (715).</p> <p>To help radiologists familiarize themselves with the CT appearance of COVID-19 infection, several online tools compiling and sharing Chest CT images of COVID-19 patients have been developed: eg. https://bit.ly/BSTICovid19_Teaching_Library; https://pubs.rsna.org/2019-nCoV#images; https://www.bsr-web.be/docs/Imaging_Coronavirus_BSR_chest.pdf; https://radiologyassistant.nl/chest/covid-19-corads-classification).</p> <p>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 (716). Inversely, negative Chest CT in PCR positive patients has also been reported (717), 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 (718). In Wang et al’s study on temporal changes of Chest CT in COVID-19 pneumonia (n=366), the extent of lung</p>

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	<p>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 (719). 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 (444). Similarly, on the "Diamond Princess cruise ship", 41 out of 76 asymptomatic cases (54%) had abnormal CT findings (720).</p> <p>Chest CT lacks however in specificity. Indeed, the typical radiological findings of COVID-19 overlap with those of other viral pneumonias. The predictive values of Chest CT will therefore depend on the phase of the epidemic as well as the level of co-circulation of other viruses such as influenza.</p>
<h3>Epidemiology</h3>	
<p>Timeline Last update 07 March 2022</p>	<p>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.</p> <p>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.</p> <p>On the 30 January 2020, the WHO declared the outbreak a public health emergency of international concern.</p> <p>In Belgium, the first confirmed case was reported on 03 February 2020, an asymptomatic person repatriated from Wuhan.</p> <p>On 22 February, the Italian authorities reported clusters of cases in Lombardy and cases in Piedmont and Veneto regions. During the following 2 weeks, several European countries, including Belgium, reported cases of COVID-19 in travelers from the affected areas in Italy, as well as cases without epidemiological links to Italy, China or other countries with ongoing transmission.</p> <p>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.</p> <p>The first COVID-19 wave in Belgium ran from March 1 to June 22, 2020. During the summer of 2020 there was an "inter-wave period", with a small surge in Antwerp. On August 31, 2020 a second wave of the epidemic initiated, followed by a third wave, powered by the emergence of the Alpha variant, that ran from February 15 to June 27, 2021. There was no clearly discernible interwave period between the second and third waves. In the summer of 2021 there was again an "interwave period", followed by a fourth wave with the Delta variant that began on October 4, 2021 and that was immediately followed on 27 December 2021 by a fifth wave caused by the Omicron variant.</p> <p>The epidemiological reports for Belgium can be found here: https://epidemiowiv-isp.be/ID/Pages/2019-nCoV_epidemiological_situation.aspx.</p> <p>For international epidemiological updates:</p> <ul style="list-style-type: none"> • WHO: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports • ECDC: https://www.ecdc.europa.eu/en/novel-coronavirus-china • John Hopkins Coronavirus Resource Center: https://coronavirus.jhu.edu/map.html • Our World in Data: Coronavirus Pandemic (COVID-19) - Statistics and Research - Our World in Data
<p>Basic reproductive number Last update</p>	<p>The basic reproductive number, the so-called R_0, of the initial Wuhan strain was thought to be between 2-4 (721,722) meaning that in a fully susceptible population, one infected individual on average infected 2-4 others in the absence of control measures. To control an epidemic, the effective reproductive (R_t) number needs to be less than one. The effective reproductive number is influenced by the level of community immunity and by measures that are put in action like social</p>

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<p>14 June 2020</p>	<p>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) (723). In the United Kingdom, "lockdown" patterns of social contact were compared to those during a non-epidemic period in a survey-based study. A 74% reduction in the average daily number of contacts observed per participant was reported. According to the authors, this would be sufficient to reduce the reproductive number from 2.6 prior to lockdown to 0.62 (95%CI 0.37-0.89) after the lockdown (724). 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) (725). The basic reproductive number of the Delta variant was higher, explaining most of its growth advantage. One study estimated the R0 to be 5, compared to 2.8 for the ancestral strain (726). On the other hand, the growth advantage of the Omicron variant is believed to be mostly a result of its lesser susceptibility to existing immunity. One modelling study estimated the R0 to be 3.6 (727).</p>
<p>Effect of climate Last update 14 July 2021</p>	<p>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 (728–730). 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 (731,732). Moreover, certain studies have considered meteorological parameters only, without correcting for other parameters impacting disease dynamics, such as population density, population age distribution, etc (733). 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 (734). Inversely, a spatio-temporal analysis exploring the effect of daily temperature on the accumulated number of COVID-19 cases in the different Spanish provinces found no evidence suggesting a reduction in case numbers at warmer temperatures. Non-meteorological factors such as population density, population by age, number of travellers were considered in the analysis (735).</p> <p>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]) (736). 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 (737). 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.</p> <p>On the other hand, difference 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 (738).</p>
<p>Special populations</p>	

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<p>Risk groups & Risk factors <i>Last update</i> 10 March 2022</p>	<p>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.</p> <p>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 (739).</p> <p>Older age: 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 (484). 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 (740). Another recent Belgian retrospective study, assessing the association between clinical data and intra-hospital mortality in older patients with COVID-19, corroborated these results. They observed a positive significant association between intra-hospital mortality and increasing age (OR= 1.09 per every year increase, 95 % CI 1.02-1.16), a positive non-significant association between age and type 2 diabetes (OR=2.75, 95%CI 1.17-6.46), and a positive non-significant association between age and acute respiratory distress syndrome (ARDS) (OR=8.67, 95%CI 3.48-21.61) (741).</p> <p>A systematic review and meta-analysis observed the isolated effect of age on hospitalization, admission to intensive care unit (ICU), mechanical ventilation and death amongst 70 studies that met the inclusion criteria. The study demonstrated an increased age-related risk of COVID-19 in-hospital mortality, case mortality and hospitalization of 5.7% (ES=1,057, 95%CI 1,038-1,054), 7.4% (ES=1,074, 95%CI 1,061-1,087) and 3.4% (ES=1.034, 95% CI 1,021-1,048) per age year, respectively, with a high quality of evidence. The impact of age appeared to be linear, hence, no age threshold at which the risk of severe disease increased has been defined (742).</p> <p>Co-morbidities: In a meta-analysis (10 articles, 76993 patients overall), the most prevalent underlying diseases found among hospitalized COVID-19 patients were <u>hypertension</u>, <u>cardiovascular diseases</u> (CVD), <u>diabetes mellitus</u>, <u>smoking</u>, <u>chronic obstructive pulmonary disease</u> (COPD), <u>malignancy</u>, and <u>chronic kidney disease</u> (743). 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%) (744).</p> <p>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) (745).</p> <p>Although less common, some studies documented an association between neurologic disorders and severe COVID-19 (746–749).</p> <p>Gender: 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) (750). 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 (751,752). Another recent meta-analysis (42 included studies) on different risk factors of COVID-19 mortality did also observed that men have a significantly higher risk of COVID-19 mortality (HR=1.45, 95%CI 1.41-1.51). There seems to be sex differences in both the adaptive and innate immune system that may account for the women advantage in coronavirus (753).</p> <p>Smoking: 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%</p>
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	<p>(65/305) of cases (754). Those results have also been corroborated by another systematic review, exploring the different risk factors for COVID-19 mortality. Indeed, when comparing smokers with non-smokers, the risk of COVID-19 mortality was significantly associated with the “smoking” status (OR=1.42, 95%CI 1.01-1.83) (753).</p> <p>Obesity: Obesity has emerged as an independent risk factor for susceptibility to and severity of COVID-19 (755,756). 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) (757)</p> <p>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]) (758). On the other hand, another review of 35 papers, also from 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 (759). Individuals of Black and Hispanic ethnicity were also more likely to be admitted to ICU.</p> <p>Health-care workers: cfr section on health-care workers in ECDC document 'Disease background of COVID-19'.</p> <p>Genetics: Genetic determinants of severe COVID-19 have been investigated. 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) (760). 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 (761,762). 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 (763). Moreover, a meta-analysis, aiming to investigate the available evidence for the genetic susceptibility to COVID-19, observed that a correlation was found between the ACE2 levels and the susceptibility to SARS-CoV-2 infection. Indeed, COVID-19 uses the angiotensin-converting enzyme 2 (ACE2) receptor for cell entry and people with ACE2 polymorphism who have type 2 transmembrane serine proteases (TMPRSS2) are at high risk of SARS-CoV-2 infection. On the other hand, patients possessing HLA-B*15:03 genotype seem to become immune to the infection (764). 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.).</p>
<p>Children Last update 11 March 2022</p>	<p>Children are less affected by COVID-19 than adults and are more likely to have mild or asymptomatic infection (765). 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 2020). A description of COVID-19 in children during the schoolyear 2020-2021 can be found here (NL/FR). Fatal outcome in children is extremely rare, as was confirmed by review of UK mortality data from the 1st year of the pandemic (March 2020-Feb 2021). (766) Of 3105 deaths in children and young people during the year, only 25 were</p>

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attributable to COVID-19. Most children who died (18/25, 72%) were >10y old and had chronic underlying conditions (19/25, 76%). The US saw a surge in pediatric hospital admissions with COVID-19 in summer 2021, coinciding with the arrival of the delta variant and very high levels of virus circulation. However, among hospitalized children and adolescents with COVID-19, the proportion with indications of severe disease remained unchanged after the delta variant became predominant. Hospitalization rates were lowest in the agegroup 5-11y. (767) With regards to “long COVID” in children, it is important to realize that symptoms like headache and fatigue are relatively prevalent even in a control group without infection. In the UK, a subsample of the population is followed up with repetitive testing and surveys for symptoms. Results indicate that 3.2% of all children 2-11 years (or their parents) old still report at least one symptom 12 weeks after infection. However, the proportion was the same in a control group without prior infection. Continuous symptoms 12 weeks after infection were reported for 0.7% of children 2-11y and 1.2% for adolescents aged 12-16y. (768) This is in line with other clinical data from the UK, indicating that only 1.8% of children still had symptoms >8 weeks after a positive COVID-19 test and that persistent symptoms could also occur in children with respiratory symptoms and a negative COVID-19 test. (518) Risk for persisting symptoms was higher in older children compared to younger children.

At the beginning of the Omicron wave (Dec 2021-Jan 2022), there were reports from several countries that young children were relatively more hospitalized, compared to adults, than in previous waves (51,769,770). However, further analyses showed that Omicron was also in children less severe than previous variants and that the relatively higher hospitalization rate was mainly a result of the lack of vaccination in young children (771-773).

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 (774-778). 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 (779-783). Mathematical modelling concluded that children are about half as likely to get infected as adults (779), a conclusion that was supported by a meta-analysis of contact tracing data by Viner et al (783). 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 (784). Several mechanisms have been proposed to explain this relative resistance, from immune imprinting by other viruses (785) to distribution, maturation, and functioning of viral receptors (786). Seroprevalence data have sometimes shown higher-than-expected antibody-detection rates but need to be interpreted with caution: see “[asymptomatic infections](#)”.

There is concern that the increased transmissibility of variants of concern would render adults and children equally susceptible. An analysis of outbreaks in daycare centres in Germany showed indeed similar secondary attack rates in adults and children with the alfa-variant (787), whilst contact tracing data from the UK showed an increase of susceptibility in all age groups, but with still a lower susceptibility in the 0-9 years old (788). A Belgian seroprevalence study in schools showed comparable infection rates in children, teachers and the general population by end of May 2021 (789).

The role of children in the transmission dynamics of SARS-CoV-2 remains much debated (790) and seems to be lower than in older children and adults (791). 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 (792). 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 (793). 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 (794). Based on contact

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tracing studies on **household transmission**, children rarely seem to be the index case of a cluster (in 8 to 10% of households) (795,796) and children rarely cause secondary cases (797,798). A 'lower risk of onwards transmission' is however not zero risk: transmission has been described from day care settings in Poland (799) and the US (800). 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 (801). In light of more transmissible variant of SARS-CoV-2, such as the Delta variant, transmissibility across all age groups has increase (791). A UK study observed a more important rise in index cases amongst at the start of the academic year 2021/2022, compared to the start of the academic year 2020/2021, which reflects the high transmissibility of the Delta variant compared to Alpha. Indeed, index cases aged 12-15 years old accounted for 34.3% of household clusters and 5-11 years old 24.3% (802). Hence, the combination of NPIs (social distancing and hand hygiene) and other measures is paramount to reduce the risk of transmission in school (791).

Contact tracing and cluster investigations in schools before lockdown done in Ireland (803), France (804,805) and New South Wales (806) reported very limited onwards **transmission in school settings**. 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 (807). 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 (808). Several additional studies have been published on the role of SARS-CoV-2 transmission among children and in schools during the second COVID-19 wave in Europe (128,808–811). Most of these studies conclude that **schools did not play a crucial role in driving the SARS-CoV-2 pandemic, and confirm earlier conclusions that the number of cases amongst students and teachers mirror trends in the community**. Research from the US suggests that school openings are not associated with increases in community transmission at low or moderate pre-existing levels of community transmission, but can be associated with increases in transmission at high levels of community transmission (812,813). On the other hand, Mensah et al. report that during a month-long lockdown in the UK in November incidence rates rapidly declined in young adults, followed by declining incidences in children in all age groups one week later. These reduction of case numbers in children was seen despite schools remaining open (814)

In conclusion: Onwards transmission from children is possible and children should be kept home when they are sick. 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. It is as of yet unclear how vaccination (and vaccination coverage being very different between children and older adults) will impact the transmission dynamics and relative importance of certain age groups.

A syndrome related to SARS-CoV-2 is identified in children. Mid-April 2020, 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 (815). The syndrome is rare and an increase in cases seem to occur weeks after the COVID-19 epidemic peak, apparently in places that are heavily affected (816). 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, shock, and development of coronary artery aneurysms. Upon comparison with previous cohorts of Kawasaki disease or Kawasaki Disease shock syndrome, differences in both clinical and laboratory features were found, including older age in MIS-C (median age 8 to11 years) and a greater elevation of inflammatory markers such as C-reactive protein. Most patients had evidence of current or prior SARS-CoV-2 infection, based on RT-PCR and/or positive SARS-CoV-2 IgG. PIMS-TS shows significant

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	<p>severity among the children requiring hospitalization, with high proportions of septic shock, cardiac involvement and admission to intensive care (816–821). Specialized care is required but survival is high (779). A higher proportion is noticed in African and Hispanic children (779).</p> <p>For information on long COVID in children, see long COVID.</p>
<p><u>Pregnant women</u> <i>Last update</i> <i>25 February 2022</i></p>	<p>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 (822). However, preliminary data from small case series, reported similar clinical characteristics in pregnant women as in the general population (823–828). These findings were then confirmed in obstetric surveillance data from the UK (829) and a prospective cohort from NYC (830). However, in summer 2020, nation-wide data from Sweden and the USA indicated that pregnant and postpartum women were at increased risk for complications and ICU admission, compared to non-pregnant women of the same age (831). 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 (832). Both studies were a clear warning signal, but also came 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. There was no information on the reason for ICU admission, which might be related to pregnancy but not necessarily to SARS-CoV-2. Finally, even though the relative risk might be increased, overall absolute risks in this age groups seemed relatively low. An update of the CDC report was published November 6th. Analysis of data on 409,462 women of reproductive age with COVID-19 of which 23,434 were pregnant, showed pregnancy not only increased risk for ICU admission (aRR 3.0 [2.6-3.4]) but also for mortality (aRR 1.7 [1.2-2.4]) (833). However, the main limitations of the data as listed above still existed and smaller studies using more detailed information sometimes reached different conclusions (834). 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 comorbidities were frequent in the included population, with 17% of the pregnant COVID+ women being obese and 5% even having a BMI >40 (835)</p> <p>In conclusion, pregnant women with SARS-CoV-2 seem to be at relatively higher risk of ICU admission, although absolute risks remain rather 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. Despite this increased risk, 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 (836).</p> <p>Risk to the fetus: In utero transmission is possible, as proven e.g. by a case from France (837).. Vertical transmission seems however extremely rare (837–840). A systematic analysis of published reports published June 2020 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 (838). 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 (841,842).</p> <p>With increasing duration of the pandemic and a shift in predominant virus variants, other risks to the unborn child have become clear. Large cohort studies e.g. from the UK (843,844) and the US (845) have shown that children of COVID+ mothers are at higher risk of preterm delivery and delivery by caesarean section. Part of these preterm deliveries are iatrogenic, to improve maternal condition and treatment. However, even women with an asymptomatic SARS-CoV-2 infection have been shown to be at higher risk of preeclampsia (846), which can require early delivery. As early as summer 2020, concerns were raised around the possibility of intrauterine growth restriction (824)</p>

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	<p>and findings of increased vasculopathy in placentas from mothers with SARS-CoV-2 (839,847). Whilst many women with SARS-CoV-2 infection in pregnancy do not show any placental abnormalities (848), a typical COVID-19 placentitis has now been described (849–851), involving increased fibrin deposition, villous trophoblast necrosis and chronic histiocytic intervillitis. These placental abnormalities are associated with an increased risk of stillbirth (844,852). In large studies from the UK (844) and the US (852), absolute risks of stillbirth were found to be respectively 0.85% and 1.27% in women with a positive SARS-CoV-2 test upon delivery, compared to 0.34% and 0.64% in SARS-CoV-2 negative women. Whilst initial analyses did not find an increased risk of stillbirth or only very slight increases (843,853), the arrival of the Delta VOC coincided with an increase of stillbirths in Ireland that raised alert (854). Indeed, current research shows that the relative risk of stillbirth is higher after infection with the Delta VOC (aRR 4.04 [3.28-4.97]) than after infection with non-Delta variants (aRR 1.47 [1.27-1.71]), after adjusting for possible confounders like age, ethnicity, socio-economic status and medical comorbidities (852). The increased risk of stillbirth exists regardless of the severity of symptoms in the pregnant women, and seems highest in the initial 2-4 weeks after infection (342,849,855).</p> <p>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 (840,856). Reassuringly, a cohort study of 706 pregnant women with SARS-CoV-2 and 1424 negative women, did not find an association between exclusive breastfeeding and infection in the neonate (846) Moreover, it has been shown that vaccine-induced SARS-CoV-2 antibodies are readily transferred within breast milk (343).</p> <p>Vaccination: see here for more info about vaccination during pregnancy.</p>
<p>Other special populations Last update 6 February 2021</p>	<p>HIV patients: The few available case-reports of SARS-CoV or MERS-CoV infection in patients with AIDS described mild disease symptoms and recovery (857,858). 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 (859–864). Similar conclusions are drawn from later matched case-control studies comparing HIV and non-HIV patients, albeit limited in size (865,866). These results and publications are mainly from Europe, USA and China.</p> <p>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 (867). 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 (868). 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 (869). 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.</p> <p>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]</p>

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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 (870).

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 (871).

Importantly, although mild presentation and recovery from COVID-19 severe disease has been described in severely immunocompromised PLWH (860,863), data is extremely scarce for this group. As advised in the above mentioned joint statement, “immune suppression, indicated by a low CD4 (<200 cells/ μ L), or not receiving ART, should be considered a risk factor [for severe COVID-19] [...]. For PLWH with low CD4 counts (<200 cells/ μ L), 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 (872,873).

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 (874–877). Most frequent cancer types reported among COVID-19 hospitalized patients are lung, breast, gastrointestinal, genitourinary, prostate and hematological (878–883). Case-fatality rate (CFR) in cancer patients with COVID-19 ranges between 11% to 32% (878–884). 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%) (880,884). Among solid cancer patients, patients with lung cancer have been shown to have the highest death rate and highest frequency of severe events (883). 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%) (885). 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 (876,882).

Two larger studies on COVID-19 in patients with **hematological malignancies** have been conducted (886,887). 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 (886). 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

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(881–884,888). On the other hand, Yang et al. describes chemotherapy as a risk factor for in-hospital death (880). Receiving radiotherapy was also suggested to be associated with increased mortality (889). The study from Dai et al. suggests that patients with surgery or immunotherapy have a higher death rate (883). A significant limitation of these studies are the small number of patients. Caution is needed to make recommendations based on limited evidence. General and cancer type specific recommendations for patient care are available at the ESMO website (<https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic>).

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 (890,891). 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] (892). A larger international survey documented disease course and outcome of 1046 COVID-19 patients with DS (893). 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;4.4) 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 (894).

Patient management

Treatment and post-exposure prophylaxis
Last update
15 March 2022

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. Guidelines on early outpatient treatment of non-severe SARS-CoV-2 infection, including the post-exposure prophylactic use of antivirals, are available at the KCE website ([FR/NL](#)).

Interim guidance for the treatment of hospitalized cases in Belgium is available ([link](#)) and includes a review of literature and a summary of the ongoing clinical trials in Belgium.

Specific national treatment guidelines are available for children ([FR/NL](#))

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 (895,896). An RCT found no impact of ACEi/ARB switch in COVID-19 (897). 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 (898). 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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