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

02 February 2022, VERSION 14

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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, Els Van Valkenborgh, Chloé Wyndham Thomas

Over **200,000** 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which discoveries are being made, certain references included are preprint papers or rapid communications that have not yet been peer-reviewed.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.

Index: (click on link to topic of interest)

Note: Highlighted sections in this document are those that have been added or updated since version 13 (26 November 2021)

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02 February 2022, VERSION 14

Pathogen

Virology
Last update
4 September 2020

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

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

Structure: Coronaviruses are minute (65-125nm in diameter) encapsulated viruses with a crown-like appearance under an electron microscope, due to the presence of spike glycoproteins on the envelope. Coronaviruses have large (26-32 kbs) single-stranded, positive-sense RNA genomes. The genome is split into 14 open reading frames, which include 16 nonstructural proteins and four structural proteins: **the spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins**. The S protein is cleaved into two subunits, S1 and S2. S1 contains the **receptor binding domain (RBD)**, and is involved in viral entry into host cells.

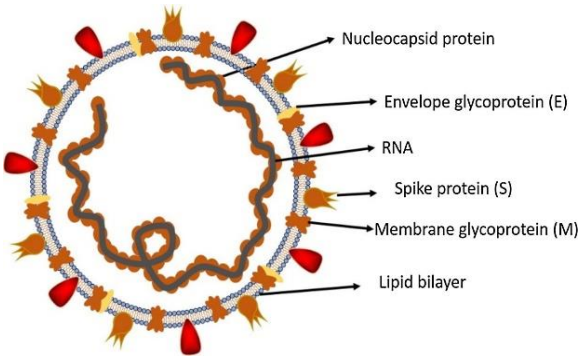

Figure 1. Structure of respiratory syndrome causing human coronavirus (2)

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

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

Genetic diversity & viral variants
Last update 02 February 2022

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

	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. **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): as SARS-CoV-2 is transmitted more rapidly than it evolves, the viral population is becoming more homogeneous. Based on CT-value analysis, it had been suggested that the G614 variant is associated with potentially higher viral loads but not with disease severity (6). Nevertheless, higher viral loads do not prove *per se* an increased transmission potential, and there was debate whether G614 was more infectious than D614, as nicely summarized by Grubaugh et al (7). Later studies demonstrated, however, shifts over time versus the G614 variant in the same geographic areas, providing more arguments for a higher transmission rate of this variant (8,9). Both these studies did not find any evidence of a significant relationship between virus genotypes and altered virulence. A study ex vivo and in vivo in rodents concluded that the D614G substitution enhanced SARS-CoV-2 infectivity, competitive fitness, and transmission in primary human cells and animal models (10). Although the G614 mutation is located in the S protein, it appeared unlikely that it would have a major impact on vaccines or drastically affect antibody-mediated immunity as the RBD of the virus is not affected by this locus. An additional study, performing phylogenetic, population genetics, and structural bioinformatics analyses of 18 514 sequences, also concluded that a vaccine candidate based on the Wuhan reference strain was likely to be efficacious against all lineages circulating at that time (11). However, it still remained unknown whether, in the long run, a gradual accumulation of mutations could result in an 'antigenic drift' of SARS-CoV-2 that could impact vaccine-effectiveness, as seen in analogy with influenza (6).
	Alpha variant. In November 2020, a new SARS-CoV-2 variant (VOC202012/01, later named 501Y.V1, lineage B.1.1.7, initially referred to as the 'UK variant', but now referred to as the Alpha variant), was identified in the United Kingdom (12,13). The variant is defined by 14 mutations resulting in amino acid changes and three deletions, some of which influence the virus's transmissibility in humans. In December 2020, the UK's New and Emerging Respiratory Virus Threats Advisory Group reported that the rate of transmission of the variant was 71%, higher than for other variants, and that it may also have a higher viral load (14). Mathematical modelling showed that an assumed 56% higher transmissibility is likely to lead to a large increase in incidence, with hospitalizations and deaths projected to reach higher levels in 2021 than were observed in 2020, even if stringent restrictions were maintained (15). A later modelling study established that the variant spread during the English lockdown (from November 5 to December 2) with an average R=1.25, against 0.85 for other variants (16), and another study that it was 75% more transmissible than other variants (17). A Danish modelling study from Denmark, on the other hand, estimated an additional transmissibility of 36% (18). A study in Canada found that the secondary attack rate was 1.31 times higher than for non-VOC cases (19). A rapid scoping review in pre-print found reported increases of risk of transmission ranging from 45% to 71% (20). The consensus is that it is about 50% more transmissible than previous variants. One of the changes with an impact on the amino acid sequence of the Alpha variant is a deletion at position 69/70 of the Spike-protein, which has been found to affect the performance of some diagnostic PCR assays that use an S gene target (TaqPath assay). By 20 December 2020 more than 97% of PCR tests in England which test negative on the S-gene target and positive on other targets were due to the 501Y.V1 variant. S gene drop-out has therefore been used as a proxy for 501Y.V1 (21). Analysis of data in the UK, as of January 10, 2021, found that the secondary attack rates for cases with S gene deletion were 25% to 40% higher than for cases without S-gene deletion (22). Initial assessment by Public Health England of disease severity through a matched case-control study reported no significant difference in the risk of hospitalisation or death compared to other variants (23). Later studies confirmed, however, an increased risk in both hospital admission and death (24).

	A study coordinated by the ECDC compared the hospitalisation rate of the B.1.1.7 variant to the rate among non-variants. The study included 19,207 cases of SARS-CoV-2 variant B.1.1.7/S gene target failure from 7 European countries and found an adjusted odds ratio for hospitalisation of 1.7 (95 % CI: 1.0 – 2.9) and for intensive care admission of 2.3 (95%CI:1.4 – 3.5) (25). The risk increase was highest in the age group 20-60 years, which confirms reports from hospitals that the variant is particularly more severe among relatively younger people. Initially, there was concern that children are, relatively compared to adults, more susceptible to the variant. A later technical brief of Public Health England, however, did not find any significant differences in age distribution by S-gene detection (as a proxy for 501Y.V1) (26). The Alpha variant rapidly became the predominant variant in Europe and worldwide (27). 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 (28). However, since then its share has declined due to the rise of the Delta variant (see below) and since August 2021 it is detected in less than 1% of all baseline surveillance samples. An additional mutation (E484K - a mutation improving the ability of the virus to evade the host's immune system) occurred in the B.1.1.7 variant and it is expected that this could lead to a reduced sensitivity to immunity induced by previous variants (29). The spread of this subtype (named B.1.1.7 with E484K) remained, however, limited.
	Beta variant. One of the mutations identified (N501Y) had also been reported in South Africa, where it arose independently of the Alpha variant (30). This variant is defined by eight mutations in the spike protein, including three substitutions (K417N, E484K and N501Y) at residues in its receptor-binding domain that may have functional importance. The variant, named 501Y.V2, lineage B.1.351, initially referred to as the 'South Africa variant' but now referred to as the Beta variant, has been reported from a total of 95 countries, but became only predominant in Southern Africa. In Belgium, the proportion of the Beta variant in the baseline surveillance initially increased to 7%, but then decreased. It was detected in only 0.5% of the samples in the period of 28 June-11 July 2021 and remained under 1% since then. The decrease is probably a result of the sharp increase of initially the Alpha variant, and later the Delta variant. Preliminary results, using a mathematical model estimated that 501Y.V2 is 50% (95%CI: 20-113%) more transmissible than previously circulating variants in South Africa (31). However, the more rapid spread could also be partially due to the reduced neutralisation by antibodies. Laboratory studies of a limited number of patients from South Africa showed indeed that the variant is less susceptible to antibody neutralization by COVID-19 donor plasma, raising concerns of a possible increased rate of SARS-CoV-2 re-infections (32,33). The above mentioned study coordinated by the ECDC, included 436 B.1.351 cases and found an adjusted odds ratio for hospitalisation of 3.6 (95 % CI: 2.1 – 6.2) and for intensive care admission of 3.3 (95%CI:1.9 – 5.7) compared to non-variant cases (25). This appears to indicate that the variant causes more severe disease.
	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 (34). It was therefore initially referred to as the 'Brazilian variant', but is now referred to as the Gamma variant. The variant has been reported from 62 countries, but only became predominant in some South American countries. Preliminary investigations in Brazil have shown a rapid increase in the proportion of cases raising similar concerns for potential increases in transmissibility or propensity for re-infection (35). A modelling study, using surveillance data from hospitalized patients in Manaus, estimated transmissibility to be 2.6 times higher than previous variants, ranking it as more transmissible than the alpha and beta variants (36). Another modelling exercise estimated a 1.4-2.2 higher transmissibility and that it evades 25-61% of protective immunity arising from infection with previously circulating variants (37). In Belgium, its proportion in the baseline surveillance samples has been fluctuating. In the period of 28 June-11 July 2021, it represented 6.3% of the baseline

	surveillance samples, and according a modelling exercise by the NRC it has 7% transmission advantage compared to the Alpha variant. Since July its presence has decreased to less than 1% because of the rise of the Delta variant. The study coordinated by the ECDC described above included 352 P.1 cases. Compared to non-variant cases, P.1 cases had an adjusted odds ratio for hospitalisations of 2.6 (95% CI: 1.4–4.8) and for intensive care admission of 2.2 (95% CI: 1.8–2.9), suggesting that also this variant causes a more severe disease pattern (25).
	Delta variant. This variant was first detected last year in India, and is a subtype of lineage B.1.617 (B.1.617.2), the other subtypes being B.1.617.1 (**Kappa variant**), and B.1.617.3 (38). 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 has rapidly spread first in India and then in the UK, at a faster rate than previous variants (39). It rapidly increased in several other countries and was by the end of June 2021 already the most common variant in the UK and in Portugal. Since then it has become the predominant variant worldwide. In Belgium, it became predominant at the beginning of July and universal in August. In the period of 16-29 August it represented 99.4% of the baseline surveillance samples. The Kappa variant has till now been identified in few samples only. The Delta variant is judged by Public Health England, with high confidence, to be 40-60% more transmissible as the Alpha variant, based on the growth rate, secondary attack rates and household transmission studies, and in-vitro increased replication in biological systems (40). An analysis of the global data submitted to GISAID, estimated the effective reproductive number for the Delta variant to be 55% (95%CI 43-68%) higher than the Alpha variant and 97% (95%CI 76-117%) higher relative to non-VOC/VOI (41,42). Early evidence from England and Scotland suggested there might be an increased risk of hospitalisation compared to Alpha cases, and this is being confirmed by a prospective cohort study in the UK that showed a twice higher risk for hospitalization among (mostly unvaccinated) patients with the Delta variant compared to patients with the Alpha variant (43). There are several sublineages of B.1.617.2 and forty-one have already been defined (AY.1 to AY.41). Two of these sublineages (AY.4 and AY.23) seem to have a relative advantage over the other AY sublineages worldwide. The AY.4 sublineage has rapidly become dominant in the UK and the AY.23 sublineage in Singapore (44). A subdivision of AY.4 (AY.4.2) is considered by Public Health England as a variant under investigation (VUI) as it seems to have a slightly higher transmissibility than the other sublineages (45). Its share is slowly increasing and it accounted at the beginning of November 2021 for about 15% of Delta cases in England (46). Preliminary analyses by PHE do 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 (47). In Europe, the AY.4.2 sublinage is considered by ECDC as a variant of interest. In Belgium, the AY.4.2 sublinage 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 is more predominant and represtents about 41% of circulating strains (28).
	Omicron variant: On November 25, 2021, a new variant was reported by the South African National Institute for Communicable Diseases, linage B.1.1.529 (48). 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 (49). 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 can 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 Vaccine Effectiveness). The variant was classified as a variant of concern by both ECDC (50) and WHO (51) on November 26, and named Omicron. Omicron has 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 has 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 (52)(53). In Belgium, Omicron represented in the period of 27/12/2021-09/01/2022 83% of the positive samples in the baseline whole genome sequencing surveillance (54). 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 (52,55–57) (58). 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 admission to intensive care. The duration of hospitalization is also shorter than for previous variants (59–63). **BA.2 sub-lineage:** The Omicron variant has three sub-lineages, BA.1, BA.2 and BA.3 (64). Initially only the BA.1 sub-lineage rapidly spread worldwide, but the BA.2 sub-lineage is quickly increasing and appearing to replace BA.1 in several countries (65). In Denmark it already overtook BA.1 as the most dominant sub-lineage, and it is also increasing in the UK and Germany, among others (66). 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 (67,68). In Denmark this is, however, only seen when the primary case is unvaccinated. In Belgium it represented 5.8% of the sequenced strains in the week of 24 January 2022. The BA.2 sub-lineage has 16 specific mutations in the spike protein, compared to BA.1, and this raises concerns that it might behave different with regards to severity and susceptibility to immunity. The UKHSA has therefore classified it as a variant under investigation. There is, however, no evidence yet that supports these concerns (69). Early observations from countries where the sub-linage has become common suggest there is no dramatic difference in severity. There is anecdotal evidence of people who became infected with BA.1 and re-infected with BA.2 shortly afterwards, possibly indicating no cross-immunity. This needs, however, to be confirmed by more data.
	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 is called the ***Epsilon variant***. The fast rise in their number, with an estimated 20% increased transmission, and evidence of reduced neutralization by convalescent and post-vaccination sera (70,71) led initially to their classification as a VOC by the US CDC. However, is has meanwhile been reclassified as a variant of interest (VOI) due to the significant decrease in the proportion nationally and available data indicating that vaccines and treatments are effective against this variant (72). The variant is mostly limited to the US and only one case has been detected in Belgium, where it is no longer considered a VOI. There are several v(73)ariants of interest, but not of concern. One such variant is lineage B.1.525 (sometimes referred to as the 'Danish variant', and now called the ***Eta variant***). It carries the same E484K-mutation as found in the Beta and Gamma variants and was first detected in the UK in February 2021. By June 27, 2021, 71 cases were described in Belgium. Another variant, first detected in Belgium and classified as VOI, is lineage B.1.214.2. (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 is rare and only considered as a variant under monitoring. A variant first detected in Columbia has lineage B.1.621 and is classified as a VOI (called the ***Mu variant***) (74). 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. According to an analysis by the NRC of data from Columbia, however, the variant will not be able to compete with the current Delta variant and is therefore not considered as an immediate public health threat for Belgium (75).
Reservoir *Last update*	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.**

3 February 2021	Whole genome sequencing has shown that SARS-CoV-2 is 96.2% identical to a bat coronavirus (Bat CoV RaTG13). This suggests that bat CoV and human SARS-CoV-2 might share the same ancestor, and that bats are a possible reservoir for the virus (1). Additional phylogenic studies are in favor of this hypothesis (76–78). 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 (79). Research is therefore ongoing to identify alternative animal reservoirs and potential intermediate hosts of SARS-CoV-2. Pangolin, snakes, and turtles have been identified as possible intermediate hosts based on the predicted interaction between the SARS-CoV-2 spike protein and host ACE2 (80). Various wild mammals, as well as cats and dogs, also have ACE2 configuration that is predicted to bind with SARS-CoV-2 S protein (81,82). A major concern is the potential formation of a non-human reservoir from where the viruses could be reintroduced once circulation of SARS-CoV-2 in humans is suppressed or even stopped. Mink farms form such a potential reservoir. Spillover of SARS-CoV-2 from humans to mink and minks to humans was first reported in the Netherlands, and later also in Spain, Italy, the USA, Sweden and Greece (83). 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 (84). 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 (85). In response, both the Netherlands and Denmark have culled all minks in the country.
Physical and chemical resistance of the virus *Last update 15 May 2020*	In the absence of any ventilation, according to a study (86), 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 (87). 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 (87,88). Soap, which dissolves the lipid bilayer of the virus, also induces SARS-CoV-2 inactivation. Several countries have looked at options for decontamination and re-use of personal protective equipment: decontamination of FFP2/N95 masks with H_2O_2 vapor in the Netherlands (89) and the USA (90) and using dry heat (30' at 65-70°C) in Germany (91). 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 (92).
Prevention	
General public *Last update 03 September 2021*	**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 (93) and has been shown in a meta-analysis to be associated with a lower risk of viral transmission (94).
Community Masks *Last update*	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

03 September 2021	coughing or sneezing, but also when breathing or speaking, though these droplets differ in size (95). **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** (96–102). **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 (103–105). **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 (102) as well as offered some protection against particles in the aerosol-range (0.05µm) (106). 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) (107) 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) (108). 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 (109). 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 (110,111). ECDC listed a number of potential risks and benefits without either recommending or discouraging the use (112). 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 (113). 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 (114). 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 (115). 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 (116).
Personal Protective Equipment *Last update 04 February 2021*	**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 (117). 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 (118). **Surgical Masks vs. FFP2** Different health care authorities have issued different advice on the recommended PPE (119), which has led to confusion. Different types of masks exist: surgical masks or the more advanced 'respirators' like FFP2/3 (standard used in the EU) or N95 (standard used in the US). FFP2 masks

sometimes come with an outlet valve, in which case they will only protect the individual wearing it but should never be given to a possible patient, as it will not protect the environment.

In the above-mentioned trial during the SARS epidemic (118), 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 (120,121). This conclusion was confirmed by a meta-analysis including six RCTs published in March 2020 by the Chinese Cochrane Center (122). Some specific evidence for SARS-CoV-2 is also available from South Korea, where 41 health care workers were unknowingly exposed to *aerosol-generating procedures* on a COVID-19 patient. Of the thirty-five HCWs (85%) that wore a surgical mask, none were infected. Reassuringly, the WHO China Joint Mission Report notes that most infected HCWs in China were infected within their households (123).

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

Therefore, **N95/FFP2 masks should be used preferentially for aerosol-generating procedures**, such as endotracheal intubation and cardiopulmonary resuscitation (124). Allthough meta-analysis of various trials still conclude that there is insufficient evidence to favour one type of mask over another in health-care settings (125) Belgian recommendations broadened the indications for use of FFP2-masks in view of rising concerns around airborn transmission, more transmissible variants and wider availability of FFP2-masks, applying the precautionary principle.

Aerosol-generating procedures
Aerosols differ from droplets because of their smaller size, which allows them to stay suspended in the air for much longer. The evidence, the best of which comes from studies of SARS-CoV, suggests a consistent association between pathogen transmission and **tracheal intubation** (126). 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 (127). 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: (119,128)

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

	Different authorities list different procedures (129). 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 (124,126,128).
Ventilation *Last update* *14 December 2020*	**Increased ventilation has been shown to reduce airborne transmission** (130). In addition to increased ventilation, experts recommend limited room occupancy, avoidance of air recirculation (use 'extraction mode when using air conditioning) and frequent breaks (131–135). If recirculation of air is necessary, HEPA filters or MERV13 can filter sufficiently small particles (132). Two-and-a-half air changes have been reported to eliminate 90% of airborne contaminants (136). Opening doors and windows can generate around 5-17 air changes per hour (ACH), but this is highly dependent on several conditions (surface of the windows, orientation, outdoor temperature and wind speed…) (130,137)**.** Use of a CO_2-sensor can help to assess whether ventilation is adequate or not. CO_2-levels should be kept below 800-1000ppm (138). This usually corresponds to the ventilation threshold set by WHO of 10 l/s/person (139). Technical guidance for maintenance of ventilation systems are available on the website of the Federation of European Heating, Ventilation and Air Conditioning Associations and the Belgian Superior Health Council also issued advice on the topic. In two pre-print articles (not peer-reviewed and with several limitations), the effect of ventilation on the risk of infection is calculated on the basis of mathematical models. For example, Dai and Zhao state that at least 3-10 ACH are required to obtain a risk of infection of <1% during a half-hour bus ride with an infected person (140). 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 (141). 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.
Chemo-prophylaxis *Last update* *7 February 2020*	**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 **(142).** Later reviews and meta-analyses conclude there is currently no evidence to recommend vitamin D supplements in primary prevention **(142,143)**. 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 **(144)**. **Hydroxychloroquine** Two randomized controlled trials published in the New England Journal of Medicine assessed the use of HCQ as prophylaxis in individuals after a high-risk exposure of COVID-19 **(145,146)**. Both trials did NOT find any benefit for HCQ but did find increased side effects. The website bcfi.be / cbip.be has a useful "COVID-19 update" section where recent information can be found.
Vaccination	
Vaccine development, authorisation and roll-out *Last update* *03 February 2022*	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) (147). According to the WHO COVID-19 candidate vaccine landscape (updated on 1 February 2022), 194 vaccines are in pre-clinical development and 140 vaccines are now in clinical development (74 in phase I or I/II, 24 in phase II or II/III, 31 in phase III clinical trials and 10 in phase IV).

	Vaccines that have received conditional authorization by the EU Commission based on evaluation and scientific review by European Medicinal Agency (EMA) are those from BioNtech-Pfizer (mRNA vaccine; Comirnaty®), Moderna (mRNA vaccine; Spikevax®), AstraZeneca-Oxford (non-replicating viral vector vaccine, ChAdOx1; Vaxzevria®), Johnson & Johnson (non-replicating viral vector, Ad26; COVID-19 Janssen vaccine®) and Novavax (protein-based subunit vaccine; Nuvaxovid®). Full updates and key documents can be found on the EMA website. All have demonstrated high vaccine-efficacy (149–152). Other vaccines are currently in rolling-review. In addition to the EMA-authorised vaccines, the WHO emergency-use list includes the COVID-19 vaccines from Serum Institute of India (non-replicating viral vector vaccine, ChAdOx1-S; Covishield®), Sinovac (inactivated adjuvanted vaccine, Vero Cell; CoronaVac®) , 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)) (153), 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 approuval was given by India to Zycov-D, a novel DNA COVID-19 vaccine. According to the WHO COVID-19 dashboard, over 10 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. 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®, Vaxzevria® and Janssen's COVID-19 Vaccine® are in use. 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. 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 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.
Vaccine effectiveness *Last update* *02 February 2022*	Many studies have by now published vaccine effectiveness (VE) results (set in "real-life settings" as opposed to clinical trials), although still mainly for Comirnaty® (Pfizer-BioNTech) and Vaxzevria® (AstraZeneca-Oxford) and from the pre-Delta era. Most of these studies have generally showed a good protection against infection (all or symptomatic) (154–177), hospitalization (155,157,162,164,171,175,177–179) and death (130,132,139,147,150). Furthermore, a majority of these studies showed substantial protection after the first dose, which further increases after the second dose (130–134,136,138,140,141,143,144,144,145,145–150,152,156–158). 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 Delta variant is good against hospitalization, similar to protection against previous variants, and against symptomatic disease. Protection after the first dose is, however, substantially lower, stressing the importance of the second dose. Protection against asymptomatic infection and transmission appears to be somewhat lower. Protection against infection (both asymptomatic and symptomatic) by the the Omicron variant, however, is substantially less than against Delta infections 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.
	Pre-Delta era 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 (184). 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 32–68) VE 14 days after the first dose and 95% (95%CI 96-97) 7 days after the second dose (185). 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 (186). A more detailed description of VE results by vaccine brand in pre-Delta era is presented below: The first large studies came from Israel. One study (Dagan et al.) looked at VE after first and second dose of **Comirnaty®** against a range of different outcomes. It found that effectiveness 21-27 days after first dose was 80% (95%CI: 59–94) for severe outcomes and 66% (95%CI: 57–73) for symptomatic infection. After a second dose, similar effectiveness was reached (severe disease 92% (95%CI: 75–100) versus symptomatic infection 94% (95%CI: 87–98)). Effectiveness in preventing death from COVID-19 was 84% (95%CI: 44–100) 21-27 days after first dose (no results for later time points available) (157). These high results for second dose effectiveness of Comirnaty® were later confirmed in a larger VE study (Haas et al.), which additionally found a 96.7% (95%CI: 96.0–97.3) effectiveness against COVID-related death ≥ 7 days after second dose (164). In a large Scottish published study by Vasileiou et al., a peak VE against COVID-19 hospitalization of 91% (95%CI: 85–94) was reached on 28-34 days after first dose administration (178). Several studies have looked at VE of Comirnaty® against asymptomatic infection. Dagan et al. reported a 90% (95%CI: 83–94) effectiveness in prevention of asymptomatic cases ≥7 days after the second dose (supplementary analysis; 3) and Haas et al. found a comparable 91.5% (95%CI: 90.7–92.2) (164). A Spanish study found VE estimates against asymptomatic infection to be in line with the estimates against all infections (175). In contrast another Spanish study found a significant lower protection against infection (66%; 95%CI 57-74) than against symptomatic COVID-19 (82%; 95%CI 74-88) among high-risk contacts (171). Initial studies assessing VE of **Vaxzevria®** focused on the first dose, because of the long delay between 1st and 2nd dose. In the aforementioned Scottish study by Vasileiou et al, VE against hospitalisation after first dose was 88% (95%CI 75-94) vs 91% (95%CI 85-94) for Comirnaty®. A study in the UK among elderly (>=80 years) found a somewhat lower effectiveness against symptomatic disease than for Comirnaty® (61% vs 70%) (155). Later studies, often covering periods during which that the Delta variant had become predominant, looked at effectiveness after 2 doses. A large test-negative case-control study in the United Kingdom (Lopez Bernal et al.) found a lower protection, albeit remaining high, against hospitalization, compared to Comirnaty®, both among Alpha infections (86%; 95%CI 53-96 vs. 95%; 95%CI 78-99) and Delta infections (92%; 95%CI 75-97 vs. 96%; 95%CI 86-99) (187). Another study from the UK found a similar protection against symptomatic disease as Comirnaty® when Alpha was predominant (97%) but less protection since Delta had become predominant (71%; 95%CI 66-74 vs. 84%; 95%CI 82-86) (188).

	Limited specific estimates for **Spikevax®** (Moderna) are available. One pre-print study in a limited number of people showed an effectiveness in line with that of Comirnaty®: 92% (95%CI: 86-96) protection against symptomatic disease and 94% (95%CI: 89–97) against hospitalization or death (177). Another, larger pre-print study found a slightly higher protection, 14 days after the second dose, by Spikevax® than by Comirnaty® against SARS-CoV-2 infection (86% (95%CI: 81-91) and 76% (95%CI: 69-81), respectively) and against hospitalization (92% (95%CI: 81-97) and 85% (95%CI: 73-93), respectively) (189). The difference in protection against infection became more pronounced in the period that the Delta variant had become predominant (76% (95%CI: 58-87) for Spikevax® and 42% (95%CI: 13-62) for Comirnaty®). Two case-control studies in the US, one among veterans and one among adults in general, found a higher VE against hospitalisation for Spikevax® than for Comirnaty® (190,191). In veterans, VE was 91.6% (95%CI: 83.5–95.7) vs. 84% (95%CI: 74.0–89.4), and in general adults 95% (95%CI: 92.97) vs. 80% (95%CI: 73-85). The latter study also assessed protection against admission at the emergency department and found a similar difference (92%; 95%CI 89–93 vs. 82%; 95%CI 81-84). Data on the COVID-19 Vaccine **Janssen®** are still scarce. A first pre-print study showed a 76.7% (95%CI: 30.3–95.3%) effectiveness against laboratory confirmed infection ≥14 days after vaccination (192). The above mentioned case-control study in the US found a substantial lower protection against hospitalization (60%; 95%CI 31-77) and admission to the emergency department (65%; 95%CI 56–72) than for Comirnaty® and Spikevax®. 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 (193).
	Beta and Gamma variant Some studies have looked specifically at effectiveness against newly emerging variants compared to previous circulating variants. 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 (194–200), Vaxzevria® elicited sera (197,201) and sera from Janssen® vaccinees (202,203). Data with regards to the neutralizing capacity against the Gamma variant were more reassuring. Two pre-prints of laboratory studies found only moderate reductions (2.6-4.8 fold) of antibody neutralizing capacity of Comirnaty®, Spikevax® or Vaxzevria® elicited sera against the Gamma variant (197,204). With regard to Janssen®, laboratory studies suggested a 3.3 to 3.6-fold reduction in neutralizing capacity of J&J vaccinees' sera (202,203), but CD8 and CD4 T cell responses seemed to not be affected (203). Caution is however needed when interpreting results of neutralization assays since correlates of protection have not yet been determined and results should be confirmed with real-life effectiveness studies. 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 (205). 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 (206), which is substantially lower than the 12 weeks used in Belgium. With regards to Comirnaty®, Pfizer claimed in a press release that it was 100% effective in preventing COVID-19 cases in South Africa, where the Beta variant was prevalent, but these results have not yet been published (207). A study in Qatar showed, however, a 15% lower VE ≥ 14 days after the second dose of Comirnaty® against the Beta variant than against the Alpha variant (208,209). In addition, an

	Israeli pre-print found that breakthrough cases, 7-13 days after the second dose, were disproportionally infected with Beta as compared to non-vaccinated cases (odds ratio 8:1), suggesting a possible reduced vaccine effectiveness (210). 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 (177). According to the phase III J&J clinical trial, efficacy was very similar in Brazil as compared to the US. But at that time 69% of cases were due to Brazilian variant of interest P.2, and not the variant of concern P.1 (Gamma).
	Vaccine effectiveness against Delta variant Initial assessments of VE against Delta were largely based on studies investigating the neutralizing ability of sera for the Delta variant (211–213) or reinfections with Delta in people previously infected with another variant (214). In June 2021, ECDC concluded that, based on the available evidence, the emergence of the Delta VOC is not associated with an increase in reinfections amongst recovered individuals infected with previously circulating SARS-CoV-2 strains and that although convalescent sera demonstrate reduced neutralisation capacity against the Delta VOC when compared to ancestral strains, they still effectively neutralise the Delta VOC in-vitro (41). Other laboratory studies have since then shown sera from persons vaccinated with Spikevax® or Janssen® to have a modestly reduced neutralizing capacity against the Delta variant (202,215,216). Evidence from real-life observational studies has meanwhile been accumulating. Interim results of a living systematic review and meta-analysis of 17 studies (217), showed a VE against any infection ranging between 49% and 82%, and a pooled VE of 66.9% (95%CI: 58.4–73.6) (218–220,188,221,189,222–225). 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) (188,224); against symptomatic infection it ranged between 56% und 87.9%, and the pooled VE was 75.7% (95%CI: 69.3–80.8) (177,187,188,218,221,224,226–228); 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) (189,222,224,225,228–230). 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. Some of these studies found only modest or no reduction in VE against symptomatic disease or hospitalization compared to previous variants after complete vaccination, but a bigger difference after only one dose, emphasising the need for a second dose (177,187,231). Based on the available evidence ECDC concluded in June 2021 that those who have only received the first dose of a two-dose vaccination course are less protected against infection with the Delta VOC than against other variants, regardless of the vaccine type but that full vaccination provides nearly equivalent protection against the Delta VOC as for the Alpha VOC (41). Some other studies in the US, not included in the above cited review, compared VE during the period that the Alpha variant was dominant with the period that the Delta variant had become dominant. The above mentioned case control study among American veterans (Bajema et al.) found no difference in protection against hospitalization between the period before (84.1%) and after the Delta variant had become predominant (89.3%) (190), and also Grannis et al. did not see a difference (191). In a letter to the editor, results of VE against symptomatic infection in a cohort of health care workers in the US are presented by calendar month. The authors found a relatively stable VE (by

	Comirnaty® or Spikevax®) during the period March-June 2021 (around 94-96%), but a sharp decrease in July (66%), the month the Delta variant had become predominant (232). A study in Houston, Texas investigated post-vaccination breakthrough infections and found that the Delta variant caused a significantly higher rate of breakthrough cases (233), possibly indicating a lesser protection. However, relatively few of the Delta breakthrough cases required hospitalization. An analysis of health records of the Veteran Health Administration in the US showed a strong decline in VE against infection between February and October 2021 from 87.9% to 48.1% (234). The decline was the greatest for the Janssen® vaccine (from 86.4% to 13.1%), compared to Comirnaty® (86.9% to 43.3%) and Spikevax® (89.2% to 58.0%). The authors contribute the decline mostly to the emergence of the Delta variant, although other factors such as a higher risk of infection or waning immunity might also have played a role.
	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 (235–237)(238). The evasion of existing immunity is further confirmed by epidemiological data from South Africa, the UK, Denmark and Canada. In the UK and South Africa, there is a marked increase in overall reinfection rates, even after adjusting for the size of the previously infected population (52,239). 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 (240). 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 wich 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 (241). 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 (242). 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 (240). The same analysis 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%(240).
	Vaccine effectiveness in the elderly and in residents of long-term care facilities If VE has been found to decline mildly but significantly with age (161), several studies have shown that high effectiveness is still achieved in the **elderly** (155,157,164,178,179,181). 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 (184). 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 (157). 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 (164). 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 (171). In a large English study effectiveness against symptomatic infection among >=80 years old was 89% 14 days after the 2nd dose of Comirnaty® (155). 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 (178). 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 (243). 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%) (190), 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) (191). 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) (160). 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 (244). 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 (175). 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 (245). 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 (246). 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.
	Vaccine effectiveness in immunocompromised patients 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 transplants (247–252); people with cancer, particularly hematologic cancers (253,254); people receiving hemodialysis for kidney disease (255,256); and people taking certain immunosuppressive medications (249,251,252). 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. 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 (257–259). Studies in the US and Israel have also found that immunocompromised persons account for a high proportion (≥40%) of infections among fully vaccinated hospitalized persons (259,260).
	Vaccine effectiveness in children and adolescents 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) (261–264). 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 (262,265). One of these studies specifically assessed neutralization capacity against the Omicron variant (264). It found that in adolescents and children the elicted 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. 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%)(266). 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 (267). 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 (268). 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 (269). No observational studies have yet assessed VE in adolescents or children against the Omicron variant.
	Effect on transmission First encouraging data on effectiveness of vaccination against transmission came from the UK. A Scottish pre-print found that household members of healthcare workers vaccinated with at least one dose of Comirnaty® or Vaxzevria® had a lower risk of documented COVID-19 compared to household members of unvaccinated healthcare workers (hazard ratio: 0.70, 95%CI: 0.63–0.78) ≥14 days after first dose (162). Several other studies showed similar effects (270–272). An analysis of contact tracing data in the Netherlands found a vaccine effectiveness against transmission (VET) to household contacts after full vaccination of 71% (95%CI: 63-77). Stratified by vaccine, VET values were estimated at 58% for Vaxzevria®, 70% for Comirnaty®, 88% for Spikevax® and 77% for Janssen®(273). 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 (193). More recent studies assessed impact on transmission in the post-Delta era. A case-control study in the UK found an adjusted OR of household transmission of the Delta variant compared to the Alpha variant of 1.64 (95%CI 1.26-2.13, p <0.001) (274), suggesting that VET might be less for the Delta

	variant. An update of the Netherlands contact-tracing data analysis mentioned above also showed a lower VET to unvaccinated household contacts during the Delta era compared to the Alpha era (275). Effectiveness of full vaccination of an index case against transmission to unvaccinated household contacts was 63% (95% confidence interval (CI): 46-75), compared to 73% in the Alpha era, and 40% (95% CI: 20-54) to fully vaccinated household contacts. An observational study in the UK assessed the secondary attack rate (SAR) in household contacts exposed to the delta variant stratified by the index cases' vaccination status and found, however, that the SAR among household contacts exposed to fully vaccinated index cases was similar to household contacts exposed to unvaccinated index cases (25% [95% CI 15–35] for vaccinated *vs* 23% [15–31] for unvaccinated) (276). 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 (277). The same authors compared household transmission by index cases infected with the BA.1 and the BA.2 Omicron sublineages (68). 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).
	Mixed dose schedules Several EU countries have adopted a mixed dose schedule (or heterologous prime-boost schedule) as a result of a halt in or age restrictions of Vaxzevria® vaccination, 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 (278–282). 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 (278,279,281,283–288). 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 (289). 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 (290). 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 (291). 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®.
	Duration of protection 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.

	A nationwide analysis in Israel of infections in people fully-vaccinated with Comirnaty®, during a period that the Delta variant had become dominant (July 2021), showed a statistically significant increase as time from second vaccine dose elapsed of the rates of both documented SARS-CoV-2 infections and severe COVID-19 (292). A large retrospective cohort study in the US found that VE of Comirnaty® against SARS-COV-2 infections (all variants) declined from 88% (95%CI 86–89) during the first month after full vaccination to 47% (95%CI 43–51) after ≥5 months (293). Against Delta infections, VE was high during the first month after full vaccination (93% [95%CI 85–97]) but declined to 53% [95%CI 39–65] at ≥4 months. Protection against COVID-19-related hospitalization did not wane over time, with overall adjusted VE estimates of 87% (95%CI 82–91) at < 1 month after being fully vaccinated, and 88% (95%CI 82–92) at ≥5 months after full vaccination. The decline was observed across age groups. In a matched test-negative, case-control study in Qatar, VE of Comirnaty® reached its peak at 77.5% (95% CI 76.4-78.6) in the first month after the second dose and declined gradually thereafter, with the decline accelerating after the fourth month to reach approximately 20% in months 5 through 7 after the second dose (294). Effectiveness against symptomatic infection waned in the same fashion. Effectiveness against any severe, critical, or fatal disease reached 96.0% (95% CI: 93.9-97.4) 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. A similar analysis of UK data, showed that VE against symptomatic disease peaked in the early weeks after the second dose then fell to 47.3% (95%CI 45.0-49.6) and 69.7% (95% CI 68.7-70.5)) by 20+ weeks against the Delta variant for Vaxzevria® and Comirnaty®, respectively (295). 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 77.0% (70.3-82.3) and 92.7% (90.3-94.6) beyond 20 weeks post-vaccination for Vaxzevria® and Comirnaty®, respectively (Delta only). Similarly, there was limited waning of vaccine effectiveness against deaths Vaxzevria® (VE 78.7% (52.7-90.4)) and Comirnaty® (VE 90.4% (85.1-93.8)) beyond 20 weeks post-vaccination for all ages. Finally, a retrospective matched cohort study in Sweden found that VE of Comirnaty® against infection waned progressively from 92% (95%CI 92-93) at day 15-30 to 47% (95%CI 39-55) at day 121-180, and to 23% (95%CI -2-41) from day 211 and onwards (296). The VE waned slightly slower for Spikevax®, estimated to be 59% (95% CI, 18-79) 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%, 95%CI -97-28), whereas VE from heterologous Vaxzevria®/ mRNA was maintained from 121 days and onwards (66% 95% CI 41-80). Overall, VE was lower and waned faster among men and older individuals. For the outcome severe Covid-19, VE waned from 89% (95%CI 82-93) at day 15-30 to 42% (95%CI, -35-75) from day 181 and onwards, with sensitivity analyses showing notable waning among men, older frail individuals, and individuals with comorbidities. Waning of immunity has further been demonstrated in several studies assessing the evolution of SARS-CoV-2 antibodies since time of vaccination (297–299). Waning over time is still more important for immunity against the Omicron variant, as is described in the section VE against the Omicron variant.
	Additional dose Data from small observational studies suggested that an additional mRNA vaccine dose in *immunocompromised people*, typically administered at least 28 days after completion of the primary vaccination, increases antibody response in solid organ transplant recipients (300–303) and hemodialysis patients (304–306). 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 (307). 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.

	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 intial doses of Comirnaty® (308) or CoronaVac (309,310). Real world data of the effect of the third dose of Comirnaty®, 5 months or more after the the second dose, are becoming avaiable from Israel and the UK. In Israel, among >=60 years old, non-booster recipients had a 11.3 (95%CI 10.4-12.3) higher risk for infection and a 19.5 (95%CI 12.9-29.5) higher risk for severe disease compared to booster recipients (311). A more recent 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 (95%CI, 11.9 to 12.9) for people 60+ years of age, 12.2 (95%CI, 11.4 to 13.1) for people aged 50-59, 9.7 (95%CI, 9.2 to 10.4) for people aged 40-49, 8.8 (95%CI, 8.2 to 9.5) for people aged 30-39, and 17.6 (95%CI, 15.6 to 19.9) for people aged 16-29 (312). The severe illness rate was 18.7-fold (95% CI, 15.7-22.4) lower for ages 60+, and 22.0-fold (95% CI, 10.3-47.0) lower for ages 40-60. For ages 60+, COVID-19 associated death rates were 14.7-fold (95% CI, 9.4-23.1) 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 7-13 days and 70-84% 14-20 days after the booster compared to two doses (313). Another retrospective analysis of healthcare service client records calculated a VE of 93% (95% CI 88–97) against hospitalization; 92% (95% CI 82–97) against severe disease; and 81% (95% CI 59–97) against COVID-19-related death (314). 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% (84.9-89.4) for those previously vaccinated with Vaxzevria® and 84.4% (82.8-85.8) for those vaccinated with Comirnaty®. Compared to unvaccinated individuals, the absolute VE against symptomatic infection was 93.1% (91.7-94.3) for those previously vaccinated with Vaxzevria® and 94.0% (93.4-94.6) for those vaccinated with Comirnaty®. The evidence on booster dose effectiveness is also supported by growing evidence with regards to waning of vaccine-induced immunity in time (see above). In October 2021, the EMA's human medicines committee has 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.
Vaccine safety *Last update* *03 February 2022*	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. 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 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 (315,316).
- 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 emphases 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. (317).
- 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 (318–320).

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 (321).Importantly, there is currently no evidence 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 May 2021, Belgium's Superior Health Council updated its recommendations for the use of mRNA vaccines in pregnant women. In these recommendations, vaccination of pregnant women was no longer limited to certain groups (e.g., health care workers at high risk of exposure and women with co-morbidities that place them in a high-risk group for severe COVID-19), but advised for all. Pregnant women thereafter became a priority group for vaccination in the country. Reassuringly, research from the

	US on more than 100,000 pregnancies did NOT show any concerns regarding spontaneous abortion and vaccination with mRNA vaccines (322). **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. Covid-19 with onset 7 days or more after the second dose was reported in 3 vaccinated children and in 16 placebo recipients (vaccine efficacy, 90.7%; 95%CI, 67.7 to 98.3) (262). 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.
Clinical Aspects	
Modes of transmission *Last update 7 July 2021*	Evidence indicates that SARS-CoV-2 is transmitted from **human to human by infectious droplets** (323). 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 (324,325). Transmission may also occur **indirectly through contaminated surfaces or fomites**, although that risk is generally considered to be low (326). Several studies have shown extensive contamination of inanimate surfaces around an infected person (327) and other respiratory illnesses and coronaviruses can spread through indirect contact (139). 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 (328,329). 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 (326,330). 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 (331–333). Especially in faeces, viral RNA seems to be present later and persists longer than in samples from the upper respiratory tract (334). **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 (331,335,336) but no cases of faeco-oral transmission have been documented (330). 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 (337). For this reason, ocular protection (goggles, faceshield) is part of the standard PPE for health care workers when in close contact with cases (cfr section PPE). For information on SARS-CoV-2 and blood donations, cfr ECDC document on COVID-19 and supply of substances of human origin.

	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 (338). 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 (339) and unclear in another (340). In the third study (341), 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 (342,343) and previous experience with SARS (344–346). 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) (347), in fitness centres during Zumba classes (348), during a choir rehearsal (349), in a restaurant without fresh air supply but air being recirculated by the air conditioning (350) or among Chinese bus passengers (351). Reassuringly, all these outbreaks involve prolonged exposure in poorly ventilated areas. One study measured the amount of aerosol particles emitted by breathing, talking and singing and found that singing and loud talking emitted about 3 times more particles than breathing, and loud singing about 5 times more (352). For the potential of intrauterine **mother-to-child transmission**, see section 'Pregnancy'.
Incubation period *Last update 13 January 2022*	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 (353–355). Larger studies and meta-analyses have since been carried out, and confirmed a median incubation period ranging between 5 and 6 days (356,357). In a study by Yang *et al* analyzing 178 cases and 131 transmission chains in Hubei province, 95 % of symptomatic cases developed symptoms within 13.7 days (95%CI 12.5–14.9) of infection (95%CI 15.9–19.7)(356). A systematic review and meta-analysis corroborate these results by demonstrating a median incubation period of 5.8 days (95%CI: 5.3-6.2) (358). 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. Analysis of 90 pairs of confirmed cases in Italy, showed a median serial interval of 6.6 days. They estimate that 95% of cases will develop symptoms within 16.1 days of symptom onset in their infector (359). A rapid review of 40 studies found a median serial interval ranging from 1.0 to 6.0 days (based on 15 estimates) (360) and a meta-analysis of 11 studies calculated a pooled estimate of 5.4 days (361). 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 (362). With the emergence of the more transmissible **Delta variant**, it has been hypothesized that the incubation period might have shortened. Different analyses (mostly pre-prints) by the same group of authors and of the same outbreak in China reported epidemiological parameters. The outbreak occurred in May-June 2021 when the Delta variant was dominant. One analysis estimated the **mean incubation period** at 5.8 days (95%CI 5.2-6.4) with 95% of the infected persons developing symptoms within 11.5 days (363). This is in line with previous estimates for the Wuhan strain as noted above. However, in another analysis, *Zhang et al*. observed a mean incubation period of 4.4 days (95%CI: 3.5-5.0) which seems slightly shorter (364). Regarding **the serial interval**, while *Kang et al*. demonstrated a time-varying serial interval which has been reduced to 4.0 days (95%CI 3.1-5.0) in mid-June 2021 (363), *Zhang et al*. observed a mean serial interval of 2.3 days (95%CI: 1.4-3.3) for the same outbreak (364). Only one other study to date, using data from 32 household transmission pairs in Singapore, observed no difference in the serial interval period of Delta vs. wild-type virus (365). Finally, *Zhang et al*. observed a **generation time** of 2.9 days (95%CI: 2.4-3.3) (364). In summary, there is currently no clear evidence to conclude that the incubation time for the delta variant would really be shorter. In contrast, higher viral load early on in the infection (and hence higher infectiousness soon after exposure) might explain the higher tranmissibility (366).

	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) (367). A household cluster investigation in the US found a median incubation period of 73 hours (+/- 3 days)(368). A study in South Korea analysed contact tracing data and estimated the mean serial interval to be 2.2 days (SD +/-1.62)(369).
Contagious period *Last update 13 January 2022*	**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 (370–377). 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 (378). 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 (347,379–381). In the study in Brunei, household attack rates of symptomatic cases were higher (14.4% [95%CI: 8.8,19.9]) than pre-symptomatic cases (6.1% [95%CI: 0.3,11.8]). A study in China looked at the ratio of pre-symptomatic versus post-symptomatic transmission and examined 468 COVID-19 cases. They reported that 12.6% of transmission occurred prior to the onset of symptoms (382). Throughout the epidemic, evidence of pre-symptomatic transmission has accumulated (373,379,382–385). 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 (386). 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 (376). A pre-print systematic review and meta-analysis of 17 studies calculated that the mean transmission time ranged from 2.91 days before symptom onset to 1.20 days after symptom onset, with a mean of 0.6 days before symptom onset (8). The authors conclude that transmission of SARS-CoV-2 is most likely in the day before symptom onset, although that in some contexts the mean could be almost three days before onset. Pre-symptomatic transmission is also illustrated by data from cluster investigations. In a detailed analysis of cases and contacts in Singapore, 7 clusters with likely pre-symptomatic transmission were identified (387). In South Korea, a large outbreak occurred among fitness instructors and attendees where the index patient developed symptoms only 3 days after the workshop (348). 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 (388). 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 (389). 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 (387). 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 (359). Currently, international guidelines (ECDC, WHO) and most country guidelines, including Belgium's, consider all potential contacts of a case from 48h before symptom onset.

End of contagious period:
Data is available from contact tracing studies, modelling of transmission and studies using viral culture. Studied populations are heterogeneous, e.g. with regards to disease severity and immunosuppression. Studies assessing viral culture generally include rather small case numbers, especially for time points long after onset of symptoms. One study in South Korea prospectively followed 21 hospitalised patients. The median time from symptom onset to viral clearance in culture was 7 days (95%CI, 5 to 10) and the latest positive viral culture was 12 days after symptom onset (390).

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

The probability of successfully culturing virus seems limited (<5%) 8-10d after symptom onset in mild-moderate cases and 14-20d (or more) in severe cases. A pre-print article does however describe a positive viral culture in a hospitalized patient (no further details) as long as 32d after symptom onset (391).

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 (392)

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

Whilst viral culture studies are difficult to interpret and all studies have important methodological limitations, the contact tracing study of Chen et al (Taiwan) is of high quality. In the study, 100 confirmed cases (of which 6 severe) and their 2,761 close contacts are followed up. Only 22 secondary 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%]) (379).

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 (393). Since then, the study with the largest sample size that has been published is by Singanayagam et al (394). 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 (defined as requiring ICU or fatal, unlike the WHO definition of 'severe disease'). 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 is low.

Data on the duration of infectiousness of the Omicron variant are still scarce. A preliminary report of the Japanese National Institute of Infectious Diseases presents the results of an examination of 83 respiratory specimes from 21 cases (19 vaccinees and 2 unvaccinated cases; 4 asymptomatic and 17 mild cases)(395). 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.

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 (396,397) and hence might be less infectious (398,399). 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 contacts of unvaccinated index cases (400–403). 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 (229,404–406). 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 (229,407,408). This was also observed in a prospective observational study in the UK, published in the Lancet Infectious Diseases (276). 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 (405), 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) (407). 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).
Asymptomatic infections *Last update 14 December 2020*	Asymptomatic infection at the time of laboratory confirmation has been reported from many settings (359,409–414), including pregnant women (415) and nursing home residents (416). The reported proportions of asymptomatic infections have varied widely, from 17.9% (410) to well over 60% (417). These differences are most likely due to incomplete symptom assessment and lack of follow-up (418) 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** (419). Another review, including only 13 studies at low risk of bias, concluded that 17% of cases remain asymptomatic (14-20%) (420). 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 (421) as well as in various other studies (420,422,423). 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 (418,424). Interestingly, an article in *Nature Communications* describes how all 3 children of two infected parents developed an antibody-response against SARS-CoV-2, although nasopharyngeal PCR swabs were repeatedly negative (425). 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 (359,371).
Symptoms *Last update 28 September 2020*	COVID-19 can present with a broad spectrum of symptoms. **The most frequent symptoms** are **fever, cough, and shortness of breath**. In the analysis of >1000 hospitalized patients from China, 44% initially presented with fever (although 89% developed fever at some point during hospitalization) and 68% with cough (355). Other symptoms included fatigue (23%), myalgia (15%), and gastrointestinal symptoms (+-8%) (426). 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 (427). 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) (428–431). Chemosensory dysfunction, such as **anosmia and dysgeusia** (either isolated or in combination with other symptoms) are common. Several studies, including a European multicenter study reported a high prevalence of both olfactory and gustatory dysfunctions in the clinical presentation of mild-to-moderate forms of COVID-19

	(432,433). Notably, anosmia has been reported after infection with other respiratory or coronaviruses (434). 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) (435). Data from more than 72,000 cases from China classified **cases as mild (81%), severe (14%), or critical (5%)** (436). Mild presentations include mild pneumonia. The actual number of mild presentations is probably higher, as due to detection policies this dataset contains only 1,2% asymptomatic cases, much lower than is currently thought to be the case (cfr. supra). The broad spectrum of atypical COVID-19 symptoms complicates the differential diagnosis with other respiratory infections. The best predictor of a COVID-19 infection are the olfactory and/or gustatory dysfunctions (437). Other symptoms that appear more frequent in COVID-19 in comparison to other respiratory infections are fever, myalgia and general malaise/fatigue (438–441). None of these symptoms was however specific enough to be used in a presumptive differential diagnosis.
Complications and mortality *Last update 9 October 2020*	As aforementioned, according to the Chinese experience, severe cases and critical cases occur in approximately 14% and 5% respectively. These cases present with severe pneumonia, septic shock, and **acute respiratory distress syndrome (ARDS)**. The critically ill patients requiring intensive care management, as with other severe viral pneumonias, present a large spectrum of complications in addition to ARDS (eg. acute cardiac injury, acute renal injury, acro-ischaemia, disseminated intravascular complications, bacterial or fungal superinfections etc.) (442,443). COVID-19 may also present with **silent hypoxia.** This phenomenon refers to a state of severe hypoxia associated with little or no respiratory symptoms such as dyspnea. It results from concomitant hypoxia and hypocapnia, a state that does not lead to the stimulus of the respiratory center of the brain. These patients go from a seemingly stable clinical state to a rapid deterioration of respiratory function within a few hours. Silent hypoxia is not unique to COVID-19, and a similar phenomenon is found with other diseases (high altitude hypoxia, heart shunt due to congenital heart disease, intra-pulmonary shunt due to lung disease etc). The exact physiopathology behind the development of hypoxia with hypocapnia in COVID-19 disease remains to be established. Although silent hypoxia is cited as a "common" clinical form, particularly in the elderly (444), only few case reports are found in the scientific literature (445,446) and testimonials from front-line physicians in the media (link). The frequency and risk factors of silent hypoxia in COVID-19 cases remain currently undefined. Evidence is emerging that COVID-19 is associated with an increased risk of **thromboembolic disease** (447,448) and a high rate of **cardiovascular complications** (431). 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) (449). In a double-center study in the Netherlands, a 31% incidence of thrombotic complications in ICU patients with COVID-19 infections is reported (450). 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% (123). In Wuhan, in admitted patients, mortality reached 25% in the middle of the epidemic (426). On March 22, the CFR in the oldest age group (>80y) in Italy was 23% (451). 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% (452). 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 (453). 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. (454) 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 0-9 y old to 16.4% in men aged 80 years and older. For Belgium, mortality is reported within the daily and weekly epidemiological reports link. In children, reports of a Kawasaki-like disease are increasingly reported, see section epidemiology > children.
Long COVID *Last update* *9 september 2021*	**Post-COVID conditions are defined as persistent or new onset symptoms or delayed or long-term complications beyond 4 weeks from the onset of symptoms** (455,456). 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 (457). The **pathophysiology is not yet fully understood** and consists probably of multiple, intertwined mechanisms (458,459). Two categories of mechanisms are distinguished (457,459): (i) direct organ damage or endothelial dysfunction caused by the virus and (ii) persisting inflammation, thrombosis and autoimmunity. About a quarter of people who have had COVID-19 exhibit symptoms for a period of 5 weeks or longer and in around **2 to 10% of patients the symptoms persist for a period of 12 weeks or longer** (457,459–461). Post-COVID conditions not only appear in patients that have been severely ill but even in patients that remained asymptomatic (456). 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 (462). The COVID Symptoms Study from King's College London found that long COVID was more likely with increasing age and body mass index and in females (461,463). 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 (464). For more information on long-COVID in children, see section children. **Many different organs are affected, in particular heart, lungs and brain** (457). 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. (457,459,463,465,466). 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 (467–472). 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) (473–476). 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 (477). 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 (458,459). 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 (478). ECDC therefore expects post-COVID to create a high burden, with additional pressures on the health care system (479). There is no simple test for **diagnosing** long COVID (457). 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 (480). Further studies are necessary to know how to **follow-up** COVID-19 patients but also to prevent these long-term consequences (481). A multidisciplinary, multispecialty approach will most probably be

	required (457,482). In December 2020, the Belgian Health Care Knowledge Centre (KCE) launched a study on the needs and follow-up of people with long COVID. Preliminary results can be found on the website of the KCE and final results are expected by October 2021.
Immunopathogenesis	
Pathogenesis *Last update 15 May 2020*	The exact pathogenesis of COVID-19 remains to be elucidated. Reviews on the topic infer from initial data on COVID-19 and knowledge from closely-related infections, such as SARS-CoV and Mers-CoV. Here we focus on the possible mechanisms involved in the development of severe disease. The virus presumably enters the body through the mucous membranes, principally the nasal and larynx mucosa, and enters the lungs through the respiratory tract. In a nonhuman primate model (cynomolgus macaque), **SARS-CoV-2 replicates efficiently in respiratory epithelial cells** throughout the respiratory tract (nasal cavity, bronchi, bronchioles, and alveoli), with replication in lower respiratory tract fitting with the development of lung disease (483). 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 (483). Persistence of **high viral loads** has been associated with disease severity (484). 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 (485). A growing body of evidence indicates a similar disease pathogenesis in SARS-CoV-2 infection. Immune injury was described in the post-mortem biopsies of a patient deceased from COVID-19 related-ARDS, in which interstitial mononuclear inflammatory infiltrates, dominated by lymphocytes, were found in both lungs (486). In addition, in a study by Huang et al, multiple cytokines and chemokines were found at higher concentrations in hospitalized COVID-19 patients than in healthy adults, among which IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNFα were significantly higher in intensive care unit (ICU) patients than non-ICU patients (487). 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 (488). 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) (486). 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 (489). **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 (426,442,490,491). In-hospital death has been associated with d-dimer concentrations greater than 1 µg/mL (odds ratio 18·42, 95%CI 2·64-128·55; p=0·0033) on admission (426). 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 (491). Moreover, as mentioned in the section "complications and

	mortality", an increased risk of thromboembolic disease and a high rate of cardiovascular complications is observed in severe COVID-19 patients. In addition, the activation of **complement pathways** may play a role in severe disease. In 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 (492). An additional mechanism of disease pathogenesis hypothesized by several authors is **antibody-dependent enhancement** (ADE) (493,494). 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 (495). Whether ADE is involved or not in SARS-CoV-2 disease pathogenesis is still unknown.
Immunity *Last update 10 September 2021*	**Humoral response:** The majority of COVID-confirmed patients develop **SARS-CoV-2 specific antibodies** (IgM, IgA and IgG) against the viral S and N protein within 1-3 weeks after symptom onset, that remain elevated after initial viral clearance. The kinetics of SARS-CoV-2 specific antibodies are developed in section on 'Serology' below. Notably, the level of the antibody response mounted after infection shows a positive correlation with the degree of disease severity (496–499). Longitudinal follow-up of COVID-19 patients has shown that antibody levels may rapidly wane, declining within 2 months after symptom onset (497,498) but thereafter remain relatively stable for 6-12 months (500–502). Type of assay used and methodological design may explain dissimilarities between studies. As Seow *et al* 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) (496). 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 (500,502,503). **Virus-specific neutralizing antibodies** (nAbs) are antibodies that not only bind to a virus, but block viral infection of the host cell. Highly effective nAbs protect against future infections and are considered as good correlates of immunity and protection after either infection or vaccination. In SARS-CoV-2, the S protein epitopes, including RBD epitopes, are the main targets of nAbs (504,505). In a rhesus-macaque COVID-19 model, titers of nAbs linearly increased after primary infection and may have contributed to the subsequent protection from reinfection observed upon a second viral challenge on day 28 (506). However, in humans, a clear relationship between the presence of nAbs and protection against reinfection by SARS-CoV-2 has not yet been established. In a study analyzing plasma samples collected from 175 recovered COVID-19 patients after mild to moderate disease, nAbs were found in a majority of patients between day 10 and 15 of disease onset. Notably, 30% of the recovered patients generated very low titers, and nAbs could not be detected in 10 patients (507). In this study and others, the magnitude of the nAb response, as for total antibody levels, correlated with disease severity (496,507). In the above mentioned longitudinal study by Seow et al, assessing the kinetics of nAbs in 65 PCR-confirmed COVID-19 cases, nAb titers peaked on average at day 23 post-onset of symptoms, and then decreased 2- to 23-fold during the 18-65 days follow up. In individuals that had developed only modest nAb titers following infection, nAbs became undetectable or approached baseline after +/- 50 days. In contrast, those with high peaks of nAb titers maintained these level for >60days (496). **Of interest is the experience we have acquired from related viral infections.** With the closely related SARS-CoV-1, antibodies (including nAbs) have been shown to persist for 1 to 2 years, possibly longer

	(508,509). In MERS-CoV patients, specific IgG antibodies were shown to persist at least one year in patients with severe disease (n=5) and in 2 out of 6 patients with mild disease (510). However, protection against reinfection, due to the limited duration or spread of these epidemics, is unknown. In contrast, antibody titers after infection with common coronaviruses (229E, NL63, OC43, HKU1) rapidly return to baseline levels, within 4 to 12 months. Reinfection with these coronaviruses are frequent, and are possible within the same year. The weak pathogenicity of these seasonal coronaviruses, with possibly an immune response restricted to the upper respiratory tract mucosa, may be the reason for short-lived immunity (511). **Cellular response:** Various studies have shown that virus-specific T cell responses can be detected in convalescent COVID-19 patients (512–521), even in seronegative patients indicating that immunity can be maintained even in absence of circulating antibodies (512,516,517,522). 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 (512,513,515,523). Looking at the T-cell subsets, CD4+ responses were established in >90 % of convalescent patients and CD8+ responses in 70% of the cases (519). Using different SARS-CoV-2 epitopes, it was shown that the strongest T-cells responses were against the spike protein (518,519), but also responses against membrane, nucleocapsid, env and ORFs were observed (512–514,517–519). Although not observed in all studies (513,524), it is interesting that in several studies T cell reactivity to SARS-CoV-2 epitopes was detected in 20-60% of healthy individuals (512,514,518–520), which is indicative of the presence of cross-reactivity due to previous infection with 'common cold' coronaviruses (Mateus et al., Braun et al, Nelde et al.). Whether the presence of cross-reactivity might influence the severity of COVID-19 disease is not clear. **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 (525). 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. In case of SARS-CoV-2 infections , **memory T cells** were shown to exist 6-7 months after infection (526). 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 (517,518,526,527). 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 (528). **Memory B-cells** also accumulate over the first months after SARS-COV-2 infection allowing for new antibodies production upon reinfection (529). Antibodies expressed by memory B-cell have somatic hypermutations leading to potentially increased potency (530). **Correlates of immune protection:** The contribution of different aspects of immune response and immune memory to the protection agains SARS CoV-2 reinfection remains unclear (529). Although antibodies are usually a reasonable correlate of antiviral immunity, and that studies suggest that neutralising antibodies are good correlates of vaccine induced immunity (531,532), 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). **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.
Re-positivity Reinfection *Last update 13 January 2022*	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. **Whilst reinfection is certainly possible, evidence is accumulating that a previous infection offers some protection against reinfection. It is still unclear how long the protection will last.**

Reported cases of reinfection: In August 2020, the first published case of a SARS-CoV-2 reinfection was reported in Hong Kong. Epidemiological, clinical, serological and genomic analyses (SARS-coronavirus-2 strains phylogenetically distinct) confirmed that the patient had a reinfection and not persistent viral shedding from the first infection (533). The first infection was a mild symptomatic episode, the second was an asymptomatic infection detected through screening upon return from travel. Since then several cases of reinfection have been described worldwide (254–258, 255).

Definition: For all these cases, reinfection was 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 (536,539). When the viruses from two episodes are associated to different clades or lineages, the evidence of reinfection is stronger (533,535,537).

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 (540). 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) (541). 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 (500). 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 (542). Higher IgG levels have been associated with severe disease, but even mild disease seems to offer good protection for at least 6-8 months (500,501,543).

Frequency: A large multi-centre prospective cohort study in the UK among 6,614 health care workers (HCW) who were either antibody positive or had a prior positive PCR/antibody test documented 44 reinfections, corresponding with 3.3 reinfections/100,000 person-days (544). 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 (95%CI 0.13-0.24).** Likewise, an adjusted hazard ratio of 0.11 (95%CI 0.03-0.44) , 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 (545). 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 (501,543,546) or retrospective designs using population-wide data (542,547–549), 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 (214) (see also section genetic diversity and variants).

Prior infection effectiveness: Immunity from infections by previous variants is less effective against reinfection with the Omicron variant. A study form the UK found that the neutralizing response in unvaccinated individuals previously infected with Delta was 29 times less potent against Omicron than against Delta (550). 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 (239). 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 (52). In the Netherlands, a multivariate analysis found an increased risk of Omicron infection in previously infected individuals compared with infected naïve individuals (OR=4.9; 95%CI 3.1-7.7) (551). 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 (552). 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 (553). Interestingly, also the neutralization of Delta increased 4.4 fold. **Infectiousness:** The potential of virus transmission from re-infected cases is currently unknown. No transmission was reported from the reinfection cases described above, but contact tracing and follow-up was not described in these studies. 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 symptomic reinfection with high viral loads within 25 days after initial infection was found to be mildly immunosuppressed (546). **Prolonged viral shedding**: Several reports showed that prolonged viral shedding occurs after SARS-CoV-2 infections, positive PCR results have been observed for up to 40 and 80 days post-initial symptom onset (554). One study even described a positive PCR result 104 days after the first positive test in an obstetric patient (555). 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 (556). 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 (556–558), but there is no established link between a weaker immunity in these cases and the re-positive test. A later meta-analysis showed that the mean shedding duration was 17 days in the upper respiratory tract (maximum shedding duration 83 days), 14,6 days in the lower respiratory tract (maximum 59 days) and 16,6 days in serum samples (maximum 60 days) (559). 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 (559). 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 (560). 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 (561).
Diagnosis and testing	
Overview *Last update* *19 April 2020*	COVID-19 is confirmed by the identification of the SARS-CoV-2 RNA in biological samples. In addition, clinical presentation (cfr. Clinical aspects), biological markers, and imagery contribute to the diagnosis of COVID-19. Nevertheless, there is currently no perfect 'gold standard test' for the diagnosis of COVID-19 to which diagnostic tools can be compared to. Reported sensitivities and specificities should be considered with caution. Moreover, the positive and negative predictive values of the test will depend on the prevalence of the virus and therefore on the stage of the epidemic. In addition, timing of testing with regards to symptom onset is an important factor to consider when comparing the diagnostic tools. Indeed, viral loads in the upper respiratory tract are highest in the day prior and initial days of symptom

	onset while Chest CT and serology appear to have increased performances later in disease. Knowing the advantages and limitations of each tool is essential, to use tests and interpret results adequately.
Laboratory findings *Last update* *8 December 2020*	In a retrospective cohort study including 191 PCR-confirmed adult inpatients (Wuhan, China), 40% had lymphopenia (< 0.8 x10^9/L), 67% had elevated Lactate deshydrogenase (LDH > 245 U/L), and 80% had >300 µg/L of serum ferritin on hospital admission (426). A systematic review and meta-analysis conducted in April 2020, observed that the most prevalent laboratory finding were increased C-reactive protein (CRP; 73.6%, 95%CI 65.0–81.3%), followed by decreased albumin (62.9%, 95%CI 28.3–91.2%), increased erythrocyte sedimentation rate (61.2%, 95%CI 41.3–81.0%), decreased eosinophils (58.4%, 95%CI 46.5–69.8%), increased interleukin-6 (53.1%, 95%CI 36.0–70.0%), lymphopenia (47.9%, 95%CI 41.6–54.9%), and increased lactate dehydrogenase (LDH; 46.2%, 95%CI 37.9–54.7%). A meta-analysis of seven studies showed that increased CRP (OR 3.0, 95%CI: 2.1–4.4), lymphopenia (OR 4.5, 95%CI: 3.3–6.0), and increased LDH (OR 6.7, 95%CI: 2.4–18.9) were significantly associated with severity (562).
RT-PCR *Last update* *9 September 2021*	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 risk. Lower respiratory tract samples are reserved for selected hospitalized or ICU cases. RT-PCR have also been used on other sample types, including blood or faecal samples, but these are not used for diagnostic work-up. **Sensitivity of RT-PCR** for the diagnosis of COVID-19 will depend on various factors, including type of specimen, timing of sampling, sampling technique, and also test kit quality. 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. • **Timing of testing:** In a literature review and pooled analysis, Kucirka *et al* analyzed the rate of false negative RT-PCR on upper respiratory tract samples of COVID-19 symptomatic patients (in- & out-patients) in relation to the number of days since exposure (563). 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 (564). • **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 (565,566), and assays have used different primers and probes. Instructions for test validation in Belgium are available in Fr and Nl.

	Specificity of RT-PCR for the diagnosis of COVID-19 is high (in the order of >99.5%) (567). With the exception of SARS-CoV, no cross-reactivity is found when tested against a large panel of microorganisms including the common human coronaviruses (568). A false positive would presumably occur only in the case that a non-positive sample is contaminated by viral material during the post-sampling processing of the test.
	Rapid RT-PCR tests: Most RT-PCR tests take 4 to 6 hours to get the result. However, certain platforms, such as GeneXpert, provide faster results (in about 15–45 minutes), and these are often referred to as 'rapid PCR tests'. Their performance in terms of sensitivity and specificity is similar to that of the standard RT-PCR tests (569), but their cost is higher.
Sample type *Last update* *02 February 2022*	Sensitivity of RT-PCR appears to be higher for lower respiratory samples than for upper respiratory tract samples (331,370,570). 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 (371–374). RT-PCR may remain positive longer in lower respiratory samples (370,570). In a prospective cohort of 67 COVID-19 pneumonia cases (Chonqing, China), median duration of SARS-CoV-2 RNA shedding was 12 days (3-38 days) in nasopharyngeal swab versus 19 days (5-37 days) in sputum. In this study, prolonged viral shedding was also observed in severe patients compared to non-severe patients (570). 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%) (571). 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. (572). For the Delta variant the sensivitiy 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 (573), 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 (574). 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 migh present earlier in the throat than in the nasal area. However, this needs to be confirmed by more extensive research. Sensitivity of RT-PCR on oral fluid samples is dicussed below.
Oral fluid samples *Last update* *9 September 2021*	**Oral fluid collection** instead of using nasopharyngeal (NPS) or oral/nasal swabs for RT-PCR has been suggested and is now used in certain circumstances. Methods vary widely: from posterior oropharyngeal fluids/saliva collected by spitting or drooling, or collection of oral fluid with pipet or special sponges. Gargling with saline solutions is another alternative that has been studied. Salivary samples can facilitate the sampling procedure, decrease discomfort of sampling, decrease exposure risks and, through self-sampling, decrease the workload of health care workers.

	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 (571,575–581). 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 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) (582). In the same study, it was suggested that the detection sensitivity was much better for saliva collection in a container compared to a saliva swab. Rao et al. demonstrated in asymptomatic persons in quarantine, a higher detection rate for SARS-CoV-2 in early morning saliva compared to NPS testing (93.1%, 149/160 vs 52.5%, 84/160, p<0.001) (583). 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 (584). One study has evaluated the suitability and sufficiency of self-collected samples. For saliva samples, clinical observers assessed that 96% of the samples were of sufficient quality for laboratory testing and quantitative laboratory assessment gave a Ct value (for RNase P) below 30 in 99% of the samples (585). 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 (587). 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 (588). 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) (589). However, the difference was less in samples with a Ct value <=25 (93.3% and 100%, respectively). Most studies, however, assessed the performance of saliva specimens among symptomatic people (hospitalized patients or people attending an OPD or an emergency department) and only few assessed performance in a context of screening asymptomatic people. Studies that included both symptomatic and asymptomatic people consistently found a lower sensitivity in asymptomatic than in symptomatic persons (590–592). 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 (593). 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 ≥ 10^4 copies/sample, sensitivity was 100% and equal to the sensitivity of the rapid Ag test on NPS. The consensus is that saliva samples are in particular of use in the context of repeated screening of asymptomatic adults, because of the good acceptability for patient and caregiver (and thus the sensitivity of a testing strategy) and because the reduced sensitivity to the individual test is compensated by the testing frequency (see further below). Saliva is also equivalent to a nasopharyngeal swab when viral load is high, such as in patients with recent onset of symptoms (<=5 days). For the use of oral fluids for rapid antigen testing see further below.

Impact on other respiratory viruses and multiplex PCR *Last update 04 February 202*	Multiplex PCRs have been used to analyze transmission patterns of different respiratory pathogens as well as to assess the extent of co-infections of SARS-CoV-2 and other common respiratory pathogens, and its impact on clinical outcomes. A study assessing the impact of SARS-CoV-2 on the prevalence of respiratory viruses in hospitalized patients, found that in March-May 2020 non-SARS-CoV-2 viruses (such as Influenza, rhinovirus, RSV, seasonal coronaviruses or parainfluenza virus) were present in only 4,1 % of the samples, while in the same period in 2019 they were detected in 54% of the patients (594). 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 (595). Reduction in the circulation of other seasonal respiratory viruses during the first peak of the epidemic was also observed in several regions worldwide (596–598). An early Italian study however did not see different trends for other respiratory viruses in March 2020 compared to the same period in previous years (599). Co-infections of SARS-CoV-2 and other respiratory viruses have been described in several reports, the extent of co-infections is variable. In most studies coinfection was found in only 1% to 2% of the samples (600,601). Some studies observed more extended cases of co-infections with bacterial pathogens (602). However, COVID-19 patients co-infected with influenza had in one study a 2.27 times greater risk of death than non-co-infected patients (603). Detecting co-infection, using a multiplex PCR, is 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.
Other Nucleic Acid Amplification Tests *09 April 2021*	There are a number of Nucleic Acid Amplification Tests (NAATs) that detect SARS-CoV-2, using a different technique than reverse transcriptase polymerase chain reaction. Most use isothermal amplification methods, such as transcription mediated amplification (TMA), strand displacement amplification (SDA) or loop-mediated isothermal amplification (LAMP), and some use CRISPR-Cas technology (604,605). Their specificity is similar to that of an RT-PCR, but their sensitivity is slightly lower (606).
Chest CT *Last update 19 April 2020*	Chest Computerized Tomography (CT) has been increasingly shown to be a useful tool for the diagnosis of COVID-19. As summarized by the European Society of Radiology, the **typical radiological findings** in the early phase of the disease are bilateral ground glass opacities, with a predominantly peripheral, sub-pleural location. Crazy paving and organizing pneumonia patterns are seen at a later stage, and extensive consolidation is associated with a poor prognosis (607). 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). **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 (608). Inversely, negative Chest CT in PCR positive patients has also been reported (609), 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 (610). In Wang et al's study on temporal changes of Chest CT in COVID-19 pneumonia (n=366), the extent of lung abnormalities on CT peaked in days 6 to 11 after symptom onset. In this study, an approximate sensitivity of 84% (95% confidence interval: 73%-92%) was estimated for illness days 0-5, against 99%

	(93%-100%) for days 6-11 (611). 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 (414). Similarly, on the "Diamond Princess cruise ship", 41 out of 76 asymptomatic cases (54%) had abnormal CT findings (612). **Chest CT lacks however in specificity**. Indeed, the typical radiological findings of COVID-19 overlap with those of other viral pneumonias. The predictive values of Chest CT will therefore depend on the phase of the epidemic as well as the level of co-circulation of other viruses such as influenza.
Serology *Last update* *13 July 2021*	Immunological assays, or serology tests, have been developed for the measurement of antibodies directed against SARS-CoV-2 proteins. Currently available assays target the main immunogenic coronavirus proteins: the N-protein , the S-protein or the Receptor Binding Domain of the S-protein (RBD). For information on use of serology as correlate of protection, see section immunity. **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) (613) indicated that: - Seroconversion rates are high, with SARS-CoV-2-specific IgG antibodies detected in over 90% of individuals at two weeks and 100% at four weeks. - Immunoglobulin M (IgM) is typically the first antibody to rise in acute infection, followed by immunoglobulin G (IgG) with IgG tending to persist much longer in the body. - The median time to antibody detection following symptom onset ranges from 5 to 17 days for IgM and 6 to 14 days for IgG. - The persistence of antibodies after COVID-19 is still unclear. As mentioned above (cfr section "Immunity"), several studies showed that anti-SARS-CoV-2 antibodies wane overtime while others found antibody persistence for at least 120 days. - Correlation between antibody levels and protection against reinfection or disease is currently unknown (499,614) Data on seroconversion in asymptomatic and pauci-symptomatic cases is emerging. Studies comparing the antibody response in hospitalized COVID-19 patients and in mild or asymptomatic cases, showed lower SARS-CoV-2-specific antibody responses in the mild or asymptomatic patients (615). **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) (616). 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 %)(617). An evaluation of COVID 19 serological assays found sensitivities ranging from 81 to 99 % and specificities ranging from 94 to 99 % (616). 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) (618). Inversely, cross-reactivity has been found when sera from SARS-CoV-2 patients are tested using SARS-CoV serological assays (619). 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 (620) published recommendations in which potential indications for serologic testing are including: 1) evaluation of patients with a high clinical suspicion for COVID-19 when molecular diagnostic testing is negative and at least two weeks have passed since symptom onset; 2) assessment of multisystem inflammatory syndrome in children; and 3) for conducting serosurveillance studies. Serological surveillance is also of crucial public health importance to monitor SARS-CoV-2 infection prevalence, i.e. the proportion of individuals in the population that have been in contact with the SARS-CoV-2 virus. Preliminary results of first sero-epidemiological population studies in EU Member States and the UK is available at https://www.ecdc.europa.eu/en/covid-19/latest-evidence/immune-responses. **Test validation :** A large number of in-house and commercial tests are being rapidly developed, of different qualities. Prior to implementation, tests must be registered and quality checked by the usual regulatory bodies (621).
Rapid Ag and Ab tests *Last update* *02 February 2022*	Rapid tests have been developed with the idea of a point-of-care approach, offering rapid results (within 10-30 minutes). Rapid tests have been developed both for the detection of antigens and for the detection of antibodies. **Rapid antigen tests**: These tests are immune-chromatographic assays, and involve the detection of SARS-CoV-2 antigen in respiratory samples. An initial test validated in Belgium in April 2020 showed a high specificity (100%), but low sensitivity (56-60%), compared to the RT-PCR (622). Some later developed tests show, however, better performance with overall sensitivities of around 70% (623,624). 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 (625). 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%)(626). 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.

	Performance varies, however, substantially between tests and some rapid Ag tests available on the Belgian market perform rather badly (627). 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 (624). In Germany, 96 of the 122 evaluated tests met the sensitivity limit of 75% with Ct<=25 (628). 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 (629–635) and some showed very disappointing results with regard to the sensitivity of rapid Ag tests on saliva (631,633–635). 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 hypothized that the presence of mucosal secretory immunoglobulins targeting SARS-CoV-2 antigens might compete with the rapid Ag test for the same target (633). An in-vitro analystic 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 (636). 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 (637). 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 (573). On the other hand, other in-vitro analytic studies did not find substantial differences in sensitivity for the detection of Omicron compared to Delta ((638–640) and several countries conducted laboratory evaluations of rapid Ag tests and reported a comparable sensitivity to that observed for previous strains (641–643). 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 rapid Ag test and the sensitivy 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) (644). In conclusion, there is currently not enough evidence that rapid Ag tests perform less well in the detection of Omicron compared to previous variants. **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 (645,646). Over 220 commercial rapid test kits have been developed from 20 countries, of variable performance (647). As with the other in vitro diagnostic medical devices developed for COVID-19 diagnosis, all rapid tests should be registered and quality checked by the usual regulatory bodies.
	Rapid antibody tests: These tests are immune-chromatographic assays developed for the detection of circulating SARS-CoV-2 antibodies. The tests provide rapid but only qualitative information (presence or not of IgM and/or IgG antibodies). The first peer-reviewed study in 397 patients with PCR-confirmed COVID-19 reported a sensitivity of 88% and a specificity of 90% (648). 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%) (647). 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.
Repetitive testing *Last update 5 Feburary 2021*	Repetitive or repeat testing in specific populations has been proposed as a strategy to early detect asymptomatic cases and thereby prevent outbreaks. Several modelling studies have demonstrated that frequent testing with a less sensitive test (rapid antigen test) or a less sensitive sample (saliva) is more effective than one-time testing with the more sensitive RT-PCR on a naso-pharyngeal sample

	(649–651). Most studies recommend a periodicity of at least 2-3 times a week (652–655), but others state that relatively infrequent testing, such as every one or two weeks, is already sufficient to keep controlled outbreaks small (656). 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 (657). Models also show that the health benefits of repeated testing with a rapid antigen test far exceed their costs (658). Studies evaluating the effect of repetitive screening in a real-life situation are, however, rare. In addition, the few available publications often focus on acceptability only. Little is, for example, known about the possible effect on behavior change as a result of knowing the test result. The current Belgian recommendations recommend it therefor only for people who come in frequent contact with people vulnerable to severe disease, such as staff in nursing homes. In certain other situations, it is considered as potentially useful but not a priority. Studies assessing the effect of regular universal testing overall conclude that it might help to reduce infections but that it would require unrealistic high testing frequencies (659,660). A modelling excercise 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 (661).
Testing sewage water *Last update* *3 February 2021*	An interesting method to early detect SARS-CoV-2 presence is through regular monitoring of sewage water. SARS-CoV-2 has been found in the faeces of infected patients in numerous studies. Although no evidence of COVID-19 transmission has been found via this route, monitoring of SARS-CoV-2 in sewage could be advantageously exploited as an early warning of outbreaks (662,663).
Epidemiology	
Overview *Last update* *01 April 2020*	COVID-19 was first identified in Wuhan City (Hubei province, China) in December 2019: on the **31 December 2019** a cluster of 27 pneumonia cases of unknown aetiology, including 7 severe cases, was reported, with a common link to Wuhan's Huanan Seafood Wholesale Market, a wholesale fish and live animal market. **By the 20 January 2020**, cases imported from China were confirmed in Thailand, Japan, and South Korea. **The first imported European case** was reported from France on the **24 January 2020**. In Germany, cases were reported on **28 January 2020**, related to a person visiting from China. On the **30 January 2020**, the WHO declared the outbreak a **public health emergency of international concern**. In Belgium, the first confirmed case was reported on **03 February 2020,** an asymptomatic person repatriated from Wuhan. **On 22 February**, the Italian authorities reported clusters of cases in Lombardy and cases in Piedmont and Veneto regions. **During the following 2 weeks**, several European countries, **including Belgium**, reported cases of COVID-19 in travelers from the affected areas in Italy, as well as cases without epidemiological links to Italy, China or other countries with ongoing transmission. On the **11 March 2020** the Director-General of the World Health Organization declared COVID-19 a **global pandemic** and on the **13 March 2020**, that **Europe was the new epicenter of the disease**. The **epidemiological reports for Belgium** can be found here: https://epidemio.wiv-isp.be/ID/Pages/2019-nCoV_epidemiological_situation.aspx. For **international epidemiological updates**: • 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

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Basic reproductive number *Last update* *14 June 2020*	The **basic reproductive number**, the so-called R0, of the virus is thought to be between 2-4 (664) meaning that in a fully susceptible population, one infected individual will on average infect 2-4 others in the absence of control measures. To control an epidemic, the effective reproductive (R_t) number needs to be less than one. The effective reproductive number is influenced by measures that are put in action like social distancing, quarantining and contact tracing. Various modelling studies have reported on the level of reduction of the reproductive number following the implementation of non-pharmaceutical interventions such as closure of schools and national lockdown (which vary from country to country). In France, lockdown measures were estimated to reduce the reproductive number from 2.90 to 0.67 (77% reduction) (665). 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 (666). 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) (667).
Effect of climate *Last update* *14 July 2021*	**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 (668–670). 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 (671,672). Moreover, certain studies have considered meteorological parameters only, without correcting for other parameters impacting disease dynamics, such as population density, population age distribution, etc (673). 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 (674). 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 (675). 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]) (676). 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 (677). The effect of weather and climate variables cannot be excluded, however, the increase in the number of cases observed during summertime in the Northern hemisphere, and especially in countries with high average ambient temperatures, demonstrates that weather and climate variables, in the absence of public health interventions, cannot mitigate the resurgence of COVID-19 outbreaks. On the other hand, 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 (678).
Special populations	
Risk groups & Risk factors *Last update* *06 February 2021*	The most important risk factors for severe disease and poor outcome are older age and the presence of comorbidities, in particular hypertension, cardiovascular diseases (CVD), diabetes mellitus, chronic obstructive pulmonary disease (COPD), malignancy, and chronic kidney disease. Other factors that have shown to increase the risk of a poor outcome are male gender, smoking and obesity. Populations with a higher risk comprise pregnant women, HIV patients and people with Down Syndrome. A systematic review of 114 articles assessing predictors of mortality in patients with COVID-19 found that older age, hypertension, and diabetes mellitus were most commonly associated with a significant increased risk of mortality, although that in the multivariate analysis, only diabetes mellitus demonstrated an independent relationship with increased mortality (679). **Older age:** has been repeatedly identified as the most important risk factor for severe COVID-19 disease. Out of a total of 44,672 confirmed cases in China (reported in China CDC Weekly), 87% of confirmed cases were aged between 30 and 79 years, and 3% were ≥80 years of age. Confirmed cases ≥80 years of age had the highest case fatality rate (CFR= 14.8%), followed by 70-79 year-olds (CFR=8.0%), and 60-69 year-olds (CFR= 3.6%) (436). In a retrospective cohort study by Zhou *et al*, including 191 hospitalized COVID-19 patients in Wuhan, multivariable regression showed increasing odds of in-hospital death associated with older age (odds ratio 1.10, 95%CI 1.03–1.17, per year increase; p=0·0043) (426). Liu *et al* have reported on another retrospective cohort study of hospitalized patients in Wuhan. Among 109 COVID-19 confirmed patients, 53 (48.6%) of them developed Acute Respiratory Distress Syndrome (ARDS). Compared with non-ARDS patients, in univariate analysis, patients with ARDS were elder (mean age, 61 years vs. 49 years; p< 0.001), and more likely to have underlying co-morbidities (680). 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 (453). 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 (681). **Co-morbidities:** In a meta-analysis (10 articles, 76993 patients overall), the most prevalent underlying diseases found among hospitalized COVID-19 patients were hypertension, cardiovascular diseases (CVD), diabetes mellitus, smoking, chronic obstructive pulmonary disease (COPD), malignancy, and chronic kidney disease (682). 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%) (683). In Liu et al's study introduced above, ARDS-patients compared with non-ARDS patients were, in univariate analysis, more likely to have coexisting diabetes (20.8% vs. 1.8%; p=0.02), cerebrovascular disease (11.3% vs. 0%; p=0.01), and chronic kidney disease (15.1% vs. 3.6%; p=0.049) (of note, malignant disorders were excluded from this study) (680). In Zhou et al's study, out of the 191 COVID-19 hospitalized patients included, 91 (48%) had a co-morbidity, with hypertension being the most common (30% of patients), followed by diabetes (19%), and coronary heart disease (8%). All these co-morbidities, as well as chronic obstructive lung disease (3% of cases) and chronic kidney disease (1% of cases) were associated with non-survival in univariate analysis, but were not associated with increased odds of in-hospital mortality with multivariable regression (426). 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) (684). Although less common, some studies documented an association between neurologic disorders and severe COVID-19 (685–688).

Gender: In the above-mentioned report from China CDC weekly, males represented 51% of the confirmed cases (M:F ratio 1.06:1). CFR for men was 2.8% versus 1.7% for women (436). In the Lombardy (Italy) outbreak, a large retrospective case-series on 1591 COVID-19 patients admitted to ICU, 82% were male (452). In Zhou et al's study, 62% of the 191 hospitalized patients were males. However, male gender was not identified as a risk factor for in-hospital death (426). Similarly, in Liu et al's study of 109 admitted COVID-19 patients, 54% were males and no association with gender was found when comparing non-ARDS and ARDS patients (680). Several other studies found a higher risk of severe outcome and/or death among male compared to female COVID-19 patients, after adjusting for other risk factors (686,689–691). 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) (692). 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 (693,694).

Smoking: Various observational studies have included "smoking" among variables assessed for association with severe COVID-19 or progression to death. However, definitions used have varied, with some researchers using "current smoking" and others "history of smoking" as potential risk factor. In Zhou et al's study described above, current smoker (versus non-smoker) was not significantly associated with in-hospital death (426). In another retrospective cohort study including 78 patients with COVID-19-induced pneumonia, an efficacy evaluation at 2 weeks after hospitalization indicated that 11 patients (14.1%) had deteriorated, and 67 patients (85.9%) had improved/stabilized. The progression group had a significantly higher proportion of patients with a history of smoking than the improvement/stabilization group (27.3% vs. 3.0%, $\chi 2 = 9.291$, $p = 0.018$). Multivariate logistic analysis indicated that, like age, history of smoking (OR, 14.285; 95%CI: 1.577–25.000; P = 0.018) was among the risk factors for disease progression (695).

A systematic review and meta-analysis of 16 articles (11.322 patients) established an increased odds for severe COVID-19 disease in patients with a history of smoking (OR=2.17; 95%CI: 1.37–3.46) and in patients currently smoking (OR=1.51; 95%CI: 1.12–2.05). In 10.7% (978/9067) of non-smokers, COVID-19 was severe, while in active smokers, severe COVID-19 occurred in 21.2% (65/305) of cases (696).

Obesity: Obesity has emerged as an independent risk factor for susceptibility to and severity of COVID-19 (689,697). 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) (698)

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]) (699). 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 (700). Individuals of Black and Hispanic ethnicity were also more likely to be admitted to ICU.

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

Genetics: Genetic determinants of severe COVID-19 are under investigation. A genome-wide association study (pre-print) comparing 1,610 COVID-19 patients with respiratory failure with the general population in Italy and Spain, reports two genetic susceptibility loci, one situated on chromosome 3 (3p21.31) and one on chromosome 9 (9q34.2) (701). The gene locus on chromosome 3 covers a cluster of several genes with potentially relevant functions in severe COVID-19, including

	a gene encoding SIT1 which functionally interacts with ACE2, and genes encoding chemokine receptors (CCR9 and CXCR6). For the gene locus on chromosome 9, the association signal was restricted to the ABO blood group gene. A blood-group-specific analysis showed a higher risk of COVID-19 respiratory failure for A-positive individuals (OR=1.45, 95%CI, 1.20 to 1.75) and a protective effect for blood group O (OR=0.65, 95%CI, 0.53), in line with previous reports (702,703). 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 (704). However, the contribution of genetic determinants to the geographical differences in the COVID-19 epidemic remain unknown, such differences being largely influenced by multiple determinants (testing strategy, reporting, non-pharmaceutical interventions, population demographics etc.)remains unknown, being largely influenced by multiple determinants (testing strategy, reporting, non-pharmaceutical interventions, population demographics etc.)
Children *Last update 21 September 2021*	**Children are less affected by COVID-19 than adults and are more likely to have mild or asymptomatic infection** (705). 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 goup. (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). 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). (706) Of 3105 deaths in children and young people during the year, only 25 were 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 admisions 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. (707) 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. (708) 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. (709) Risk for persisting symptoms was higher in older children compared to younger children. **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 (710–714). 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 (715–719). Mathematical modelling concluded that children are about half as likely to get infected as adults (715), a conclusion that was supported by a meta-analysis of contact tracing data by Viner et al (719). 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 (720). Several

mechanisms have been proposed to explain this relative resistance, from immune imprinting by other viruses (721) to distribution, maturation, and functioning of viral receptors (722). 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 show indeed similar secondary attack rates in adults and children with the alfa-variant (723), whilst contact tracing data from the UK show an increase of susceptibility in all age groups, but with still a lower susceptibility in the 0-9 years old (724). A Belgian seroprevalence study in schools showed comparable infection rates in children, teachers and the general population by end of May 2021 (725).

The role of children in the transmission dynamics of SARS-CoV-2 remains much debated (726) **although there exists a consensus that young children are not the drivers of transmission** (727). 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 (728). 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 (729). 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 (730). Based on contact tracing studies on **household transmission**, children rarely seem to be the index case of a cluster (in 8 to 10% of households) (731,732) and children rarely cause secondary cases (733,734). A 'lower risk of onwards transmission' is however not zero risk: transmission has been described from daycare settings in Poland (735) and the US (736). 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 (737).

Data on **transmission in school settings** is increasing. Contact tracing and cluster investigations in schools before lockdown done in Ireland (738), France (739,740) and New South Wales (741) report very limited onwards transmission. Finland and Sweden have very similar schooling systems but Sweden decided to keep primary schools open (pupils <15y). A comparison between both countries did not show any measurable impact of the school closure on the number of laboratory-confirmed cases in children (742). 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 (743). 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 (743–747). 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 (748,749). 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 (750)

In conclusion: children, especially in primary school, do not seem to be the drivers of the epidemic. Onwards transmission is however possible and children should be kept home when they are sick or when there is a COVID-infection in the household. It is important that mitigation measures are in place in schools. Adolescents (16-18y) seem to spread the virus in the same way as adults. 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, 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 (751). 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 (752). 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 severity among the children requiring hospitalization, with high proportions of septic shock, cardiac involvement and admission to intensive care (752–757). Specialized care is required but survival is high (715). A higher proportion is noticed in African and Hispanic children (715).
Pregnant women *Last update* *04 February 2021*	**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 (758). However, preliminary data from small case series, reported similar clinical characteristics in pregnant women as in the general population (759–764). These findings were then confirmed in obstetric surveillance data from the UK (765) and a prospective cohort from NYC (766). However, nation-wide data from Sweden and the USA indicated that pregnant and postpartum women are at increased risk for complications and ICU admission. In Sweden, out of 53 women that were admitted to ICU with SARS-CoV-2, 13 were pregnant (of which 7 required invasive mechanical ventilation). The risk of requiring ICU admission was significantly higher for pregnant women compared to non-pregnant women of the same age (767). Likewise, the US CDC analyzed data on 8,207 pregnant women and found pregnancy to be related with a relative risk of 1.5 [1.2-1.8] for ICU admission, after adjusting for age, presence of underlying medical conditions (yes/no) and race/ethnicity (768). Importantly, there was no increased mortality. Whilst these findings warrant further caution regarding COVID-19 in pregnancy, both studies come with important limitations. The Swedish report included only small numbers of women requiring ICU. In the CDC registry, data was missing on many variables, and info on pregnancy was only available for 28% of women in reproductive age. Both registries did not have data on the reason for ICU admission, which might be related to pregnancy but not necessarily to SARS-CoV-2. Moreover, based on changes in physiology, women would be deemed most at risk in the 3rd trimester of pregnancy but none of the registers accounted for gestational age, and pregnant women in ICU were as early as 13th weeks post-menstrual age. Finally, even though the relative risk might be increased, overall absolute risks in this age groups seem low. An update of the CDC report was published November 6th. The report includes data on 409,462 women of reproductive age with COVID-19 (symptoms and positive test) of which 23,434 were pregnant (769). This time, not only an increased risk was found for ICU admission of pregnant women vs. non-pregant women (aRR 3.0 [2.6-3.4]) but also for mortality (aRR 1.7 [1.2-2.4]). However, the main limitations of the data still exist: information on pregnancy status is missing for 64.4% of women in reproductive age and there is no information on reason for hospital/ICU admission (i.e. COVID-related vs. pregnancy related). A smaller observational cohort, also from the US, including 3,374 pregnant women of which 252 SARS-CoV+, reported that only 5% of women were hospitalized for COVID-19 reasons, which was similar to the reported hospitalization rate of non-pregnant women in the CDC report (770). Finally, an analysis of administrative data from the US (using ICD-10 codes and reimbursement codes) compared outcomes in 400,066 pregnant women without COVID-19 with 6,380 women with COVID-19. Although absolute risks were low, an increased risk was noted for thrombotic events, ICU admission and mechanical ventilation in the women with COVID-19. Of note is that the comorbidities were frequent in the included population, with 17% of the pregnant COVID+ women being obese and 5% even having a BMI >40 (771)

	In conclusion, pregnant women with SARS-CoV-2 seem to be at relatively higher risk of ICU admission, although absolute risks are low. As with non-pregnant women, risk factors like pre-existing comorbidities and age play a role. Based on experience with other respiratory infections and physiological changes, the highest risk would be expected in the third trimester. Of note is that, like the non-pregnant population, many pregnant women will have a mild or even completely asymptomatic course of the disease, as was shown again by e.g. a seroprevalence study from Madrid (772). **Risk to the fetus:** In utero transmission is possible, as proven by a case from France (773). After a cesarean delivery for fetal distress at 35w5d in a symptomatic SARS-CoV-2+ mother, a neonate was born with positive RT-PCR on cord blood, BAL and naso-pharyngeal swab. Placental histology and amniotic liquid also showed presence of SARS-CoV-2. The neonate was initially admitted to NICU and intubated but discharged at day 18 of life with a normal follow-up visit at 2 month of life. **Whilst possible, vertical transmission seems however extremely rare** (773–776). A systematic analysis of published reports identified a total of 655 women and 666 infants for which data was available. They found a total of 28 neonates, almost all asymptomatic, for which vertical transmission might have been possible, although they hypothesize that some false-positive nasopharyngeal swabs might be reported due to contamination by maternal stool (774). 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 (777,778). Pre-term and cesarean delivery rates seem related to geographical differences rather than being a result of COVID-19 (779). Some authors have warned for the possibility of intrauterine growth restriction (760), a concern that is strengthened by the findings of increased vasculopathy in placentas from mothers with SARS-CoV-2 (775,780). **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 (776,781).
Other special populations *Last update* *6 February 2021*	**HIV patients:** The few available case-reports of SARS-CoV or MERS-CoV infection in patients with AIDS described mild disease symptoms and recovery (782,783). 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 (784–789). Similar conclusions are drawn from later matched case-control studies comparing HIV and non-HIV patients, albeit limited in size (790,791). These results and publications are mainly from Europe, USA and China. The largest study on PLWH in Europe to date is from a Spanish cohort of 77,590 HIV positive persons under antiretroviral therapy (ART), among which 236 were diagnosed with PCR-confirmed COVID-19 between February and mid-April 2020. After standardization to the age and sex distribution of Spain, the risk in HIV-positive persons for COVID-19 diagnosis was 30/10 000 and 3.7/10 000 for COVID-19 death. In comparison, risk of COVID-19 diagnosis and death in the Spanish general population aged 20 to 79 years during the same period was 42/10 000 (33/10 000 when excluding healthcare workers) and 2.1/10 000, respectively. The risks of COVID-19 diagnosis, hospitalization, ICU admission, and death in the ART-receiving PLWH were greater in men and those older than 70 years, consistent with the age and sex-patterns reported for HIV-negative persons. Also, the risk for hospitalization was lower in patients receiving TDF/FTC (tenofovir disoproxil fumarate/emtricitabine) based ART versus those receiving other regimens, a result warranting further investigation due to possible confounders, particularly co-morbidities, not captured in the study (792). 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 (793). 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 (794). The authors concluded that evidence is emerging that suggests a moderately increased risk of COVID-19 mortality amongst PLWH, and that further investigation is warranted.

In a population cohort study from the Western Cape Province of South Africa, in adjusted analysis, HIV increased the risk of COVID-19 mortality by a factor of 2.14 (95%CI [1.70; 2.70]), with similar risks across strata of viral load and immunosuppression. Current and previous tuberculosis also increased COVID-19 mortality risk (adjusted hazard ratio: 2.70 [1.81; 4.04] and 1.51 [1.18; 1.93] respectively). Authors concluded that, although the HIV-associated risk of COVID-19 death may be over-estimated due to residual confounding (co-morbidities, socio-economic status), people with HIV should be considered as a high-risk group for COVID-19 management. Of note, if the larger prevalence of HIV in Africa permits such studies with higher participant numbers, results may not be transposable to Europe, due to multiple differences in population characteristics (795).

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 (796).

Importantly, although mild presentation and recovery from COVID-19 severe disease has been described in severely immunocompromised PLHIV (785,788), data is extremely scarce for this group. As advised in the above mentioned joint statement, "*immune suppression, indicated by a low CD4 (<200 cells/µL), or not receiving ART, should be considered a risk factor [for severe COVID-19] […].For PLWH with low CD4 counts (<200 cells/µL), or who experience a CD4 decline during a COVID-19 infection, remember to initiate opportunistic infection (OI) prophylaxis. This is not aiming at preventing a more severe course of COVID-19 but rather complications through additional OIs*".

Finally, concerns have been raised with regards to the impact the COVID-19 outbreak on the HIV continuum of care, with risks of limited access to testing, care and treatment, related to lockdown measures (797,798).

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 (799–802). Most frequent cancer types reported among COVID-19 hospitalized patients are lung, breast, gastrointestinal, genitourinary, prostate and hematological (803–808). Case-fatality rate (CFR) in cancer patients with COVID-19 ranges between 11% to 32% (803–809). 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%) (805,809). Among solid cancer patients, patients with lung cancer have been shown to have the highest death rate and highest frequency of severe events (808). 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%) (810). 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 (801,807).

Two larger studies on COVID-19 in patients with **hematological malignancies** have been conducted (811,812). 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 (811). 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 (806–809,813). On the other hand, Yang et al. describes chemotherapy as a risk factor for in-hospital death (805). Receiving radiotherapy was also suggested to be associated with increased mortality (814). The study from Dai et al. suggests that patients with surgery or immunotherapy have a higher death rate (808). 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 (815,816). 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] (817). A larger international survey documented disease course and outcome of 1046 COVID-19 patients with DS (818). 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 (819).
Patient management	
Treatment *Last update* *4 September 2020*	**Symptomatic and optimal supportive care** is the mainstay of treatment for COVID-19. In addition to standard care (e.g. antipyretics, fluid management, treatment of co-infections or superinfection) etc), specifics are required with regards to **preventive anticoagulation** (see recommendations BSTH) and **oxygenation** (see recommendations: hospital-setting FR/NL, ambulatory FR/NL). Self-medication & the interruption of chronic treatments without medical advice is strongly discouraged **Multiple treatment strategies, including re-purposing of older drugs, are under investigation. An interim guidance for the treatment of hospitalized cases in Belgium is available** (link) and includes a review of literature and a summary of the ongoing clinical trials in Belgium. Drugs covered in the document are corticosteroids, remdesivir, hydroxychloroquine, lopinavir/ritonavir, remdesivir, favipiravir, camostat mesylate, immunomodulatory agents (eg. anti-IL6, anti-IL-1), convalescent plasma, interferons, monoclonal antibodies, baricitinib, azithromycin, interferons, ivermectin, colchicine and aspirin. **Specific national treatment guidelines are available for children** (Traitement et prise en charge de l'enfant atteint de la COVID-19: Particularités pédiatrique; Opvang en behandeling van kinderen met COVID-19 gerelateerde ziekte) 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 (820,821). An RCT found no impact of ACEi/ARB switch in COVID-19 (822). 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 (823). 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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