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

26 November 2021, VERSION 13

Disclaimer :

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which discoveries are being made, certain references included are preprint papers or rapid communications that have not yet been peer-reviewed.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

Pathogen
- Virology
  - Taxonomy
  - Structure
  - Cell entry and viral replication
- Genetic diversity & viral variants
  - Pre-VOC
  - Alpha
  - Beta
  - Gamma
  - Delta
  - Omicron
  - Other variants
- Reservoir
- Physical and chemical resistance

Prevention
- General public
- Community Masks
- Personal Protective Equipment
  - Health Care Workers
  - Surgical verses FFP2 masks
  - Aerosol-generating procedures
- Ventilation
- Chemoprofylaxis
  - Vitamin D
  - Hydroxychloroquine

Vaccination
- Vaccine development, authorisation and roll-out
- Vaccine effectiveness
  - Pre-Delta era
  - Beta and Gamma variant
  - Vaccine effectiveness against Delta variant
  - Elderly and nursing home residents
  - Immunocompromised people
  - Effect on transmission
  - Mixed doses schedules
  - Duration of protection
  - Additional dose
- Vaccine safety

Clinical aspects
- Modes of transmission
  - Droplets
  - Fomites
  - Faeco-oral
  - Airborne
  - Mother-to-child
- Incubation period
- Contagious period
  - Beginning of contagious period
  - End of contagious period
  - Infections post-vaccination
- Asymptomatic infections
- Symptoms
- Complications and mortality
- Long COVID

Immuno-pathogenesis
- Pathogenesis
- Immunity
- Reinfection

Diagnosis and testing
- Overview
- Laboratory findings
- RT-PCR
- Impact on other respiratory viruses and multiplex PCR
- Other Nucleic Acid Amplification Tests
- Oral fluid samples (saliva…)
- Chest CT
- Serology
- Rapid tests
- Repetitive testing
- Testing sewage water

Epidemiology
- Overview
- Basic reproductive number
- Effect of Climate

Special populations:
- Risk groups and risk factors (age, gender, co-morbidities, smoking, genetics etc.)
- Children
- Pregnant women
  - Disease severity
  - Risk to the fetus
  - Breastfeeding
- Other special populations
  - HIV patients
  - Cancer patients
  - People with Down Syndrome

Patient management

References

Note: Highlighted sections in this document are those that have been added or updated since version 12 (22 September 2021)

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

26 November 2021, VERSION 13

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.

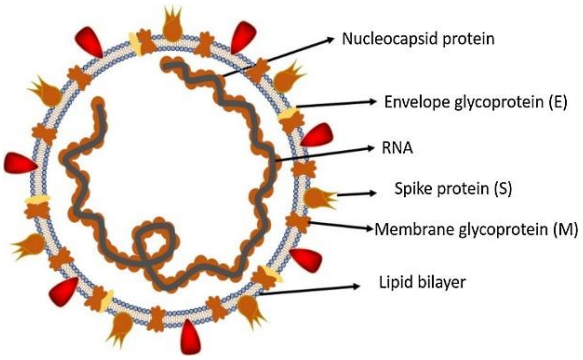

Figure 1. Structure of respiratory syndrome causing human coronavirus (2)

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 26 November 2021

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 in the pipeline or drastically affect antibody-mediated immunity as the RBD of the virus is not affected by this locus. An additional study, performing phylogenetic, population genetics, and structural bioinformatics analyses of 18 514 sequences, also concluded that a vaccine candidate based on the Wuhan reference strain was likely to be efficacious against all lineages circulating at that time (11). However, it still remained unknown whether, in the long run, a gradual accumulation of mutations could result in an 'antigenic drift' of SARS-CoV-2 that could impact vaccine-effectiveness, as seen in analogy with influenza (6).
	Alpha variant. In November 2020, a new SARS-CoV-2 variant (VOC202012/01, later named 501Y.V1, lineage B.1.1.7, initially referred to as the 'UK variant', but now referred to as the Alpha variant), was identified in the United Kingdom (12,13). The variant is defined by 14 mutations resulting in amino acid changes and three deletions, some of which influence the virus's transmissibility in humans. In December 2020, the UK's New and Emerging Respiratory Virus Threats Advisory Group reported that the rate of transmission of the variant was 71%, higher than for other variants, and that it may also have a higher viral load (14). Mathematical modelling showed that an assumed 56% higher transmissibility is likely to lead to a large increase in incidence, with hospitalizations and deaths projected to reach higher levels in 2021 than were observed in 2020, even if stringent restrictions were maintained (15). A later modelling study established that the variant spread during the English lockdown (from November 5 to December 2) with an average R=1.25, against 0.85 for other variants (16), and another study that it was 75% more transmissible than other variants (17). A Danish modelling study from Denmark, on the other hand, estimated an additional transmissibility of 36% (18). A study in Canada found that the secondary attack rate was 1.31 times higher than for non-VOC cases (19). A rapid scoping review in pre-print found reported increases of risk of transmission ranging from 45% to 71% (20). The consensus is that it is 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 raises 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 are known to affect transmissibility and immune evasion (such as K417N, E484A, N501Y, T478K and P681H), but many others have been rarely observed until now. By November 25, 77 cases had been declared from South Africa and 6 from Botwana (50). In South Africa it is rapidly replacing the Delta variant and probably at the cause of a recent increase in the number of daily cases. Two cases of the variant were also detected in Hong Kong and in Israel, in a vaccinated travelers returning from Malawi (51). The variant was classified as a variant of concern by both ECDC (52)and WHO (53) on November 26, and named Omicron.

	On November 26, the variant was detected in Belgium in a traveler returning from Egypt (28).
	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 (54,55) 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 (56). 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 variants 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***) (57). 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 (58).
Reservoir *Last update* *3 February 2021*	Like for previous invasive coronaviruses, such as SARS-or MERS-Cov, **SARS-CoV-2 is believed to have a zoonotic origin and to result from a cross-species transmission.** Whole genome sequencing has shown that SARS-CoV-2 is 96.2% identical to a bat coronavirus (Bat CoV RaTG13). This suggests that bat CoV and human SARS-CoV-2 might share the same ancestor, and that bats are a possible reservoir for the virus (1). Additional phylogenic studies are in favor of this hypothesis (59–61). 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 (62). 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 (63). Various wild mammals, as well as cats and dogs, also have ACE2 configuration that is predicted to bind with SARS-CoV-2 S protein (64,65). 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 (66). 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 (67). 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 (68). In response, both the Netherlands and Denmark have culled all minks in the country.
Physical and chemical resistance of the virus	In the absence of any ventilation, according to a study (69), 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

Last update 15 May 2020	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 (70). 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 (70,71). 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 (72) and the USA (73) and using dry heat (30' at 65-70°C) in Germany (74). 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 (75).
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 (76) and has been shown in a meta-analysis to be associated with a lower risk of viral transmission (77).
Community Masks *Last update 03 September 2021*	Because of the possibility of asymptomatic and especially pre-symptomatic transmission face masks have been recommended. In addition to offering some protection to the wearer, they act as source control, i.e. to prevent spread from asymptomatic individuals. Droplets are emitted not only when coughing or sneezing, but also when breathing or speaking, though these droplets differ in size (78). **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** (79–85). **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 (86–88). **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 (85) as well as offered some protection against particles in the aerosol-range (0.05µm) (89). 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) (90) 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) (91). 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 (92). 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 (93,94). ECDC listed a number of potential risks and benefits without either recommending or discouraging the use (95). 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 (96). 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 (97). 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 (98). 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 (99).
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 (100). 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 (101). **Surgical Masks vs. FFP2** Different health care authorities have issued different advice on the recommended PPE (102), 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 (101), 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 (103,104). This conclusion was confirmed by a meta-analysis including six RCTs published in March 2020 by the Chinese Cochrane Center (105). 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 (106). 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 (77). 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 (107). Although meta-analysis of various trials still conclude that there is insufficient evidence to favour one type of mask over another

	in health-care settings (108) 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** (109). 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 (110). 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: (102,111) • 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 (112). 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 (107,109,111).
Ventilation *Last update* *14 December 2020*	**Increased ventilation has been shown to reduce airborne transmission** (113). In addition to increased ventilation, experts recommend limited room occupancy, avoidance of air recirculation (use 'extraction mode when using air conditioning) and frequent breaks (114–118). If recirculation of air is necessary, HEPA filters or MERV13 can filter sufficiently small particles (115). Two-and-a-half air changes have been reported to eliminate 90% of airborne contaminants (119). 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…) (113,120). 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 (121). This usually corresponds to the ventilation threshold set by WHO of 10 l/s/person (122). 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 (123). 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 (124). 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 **(125).** Later reviews and meta-analyses conclude there is currently no evidence to recommend vitamin D supplements in primary prevention **(125,126)**. 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 **(127)**. **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 **(128,129)**. 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* *12 November 2021*	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) (130). According to the WHO COVID-19 candidate vaccine landscape (updated on 9 November 2021), 194 vaccines are in pre-clinical development and 130 vaccines are now in clinical development (71 in phase I or I/II, 19 in phase II or II/III, 28 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®) and Johnson & Johnson (non-replicating viral vector, Ad26; COVID-19 Janssen vaccine®). Full updates and key documents can be found on the EMA website. All have demonstrated high vaccine-efficacy (132–134). 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)) (135), 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 7 billion COVID-19 vaccine doses have now been administered worldwide and more than three 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. Belgium plans to roll-out out booster doses for HCW starting second half of November and a national plan to implement booster doses to the whole 18+ population is currently in development. 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 20 September 2021*	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) (136–159), hospitalization (137,139,144,146,153,157,159–161) 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)). Evidence on protection against the Delta variant is still accumulating. Available results show a good protection 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.
	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 (166). 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 (167). 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 (168). 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) (139). 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 (146). 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 (160). 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) (146). A Spanish study found VE estimates against asymptomatic infection to be in line with the estimates against all infections (157). 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 (153). 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%) (137). 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) (169). 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) (170). 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 (159). 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) (171). 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® (172,173). 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 (174). 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 (175).
	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 (176–182), Vaxzevria® elicited sera (179,183) and sera from Janssen® vaccinees (184,185). 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 (179,186). With regard to Janssen®, laboratory studies suggested a 3.3 to 3.6-fold reduction in neutralizing capacity of J&J vaccinees' sera (184,185), but CD8 and CD4 T cell responses seemed to not be affected (185). 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 (187). 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 (188), 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 (189). 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 (190,191). 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 (192). 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 (159). 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 (193–195) or reinfections with Delta in people previously infected with another variant (196). 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 (184,197,198). Evidence from real-life observational studies has meanwhile been accumulating. Interim results of a living systematic review and meta-analysis of 17 studies (199), showed a VE against any infection ranging between 49% and 82%, and a pooled VE of 66.9% (95%CI: 58.4–73.6) (200–202,170,203,171,204–207). 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) (170,206); against symptomatic infection it ranged between 56% und 87.9%, and the pooled VE was 75.7% (95%CI: 69.3–80.8) (159,169,170,200,203,206,208–210); 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) (171,204,206,207,210–212). 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 (159,169,213). 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%) (172), and also Grannis et al. did not see a difference (173). 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 (214). A study in Houston, Texas investigated post-vaccination breakthrough infections and found that the Delta variant caused a significantly higher rate of breakthrough cases (215), 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% (216). 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 in the elderly and in residents of long-term care facilities If VE has been found to decline mildly but significantly with age (143), several studies have shown that high effectiveness is still achieved in the **elderly** (137,139,146,160,161,163). 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 (166). 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 (139). 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 (146). 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 (153). In a large English study effectiveness against symptomatic infection among >=80 years old was 89% 14 days after the 2nd dose of Comirnaty® (137). 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 (160). 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 (217). 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%) (172), 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) (173). 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) (142). 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 (218). 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 (157). 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 (219). 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 (220). 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 (221–226); people with cancer, particularly hematologic cancers (227,228); people receiving hemodialysis for kidney disease (229,230); and people taking certain immunosuppressive medications (223,225,226). 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 (231–233). 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 (233,234).
	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 (144). Several other studies showed similar effects (235–237). 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®(238). 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 (175). 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) (239), 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. 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) (240).
	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 (241–245). 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 (241,242,244,246–251). 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 (252). 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 (253). 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 (254). 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 (255). 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 (256). 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 (257). 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 (258). 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 (259). 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 (260–262).
	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 (263–266) and hemodialysis patients (267–269). 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 (270). 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® (271) or CoronaVac (272,273). 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 (274). 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 (275). 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 (276). 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 20 September 2021*	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 (277,278). • 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 in younger adult men. Acute clinical courses have been generally mild. Follow-up is ongoing to identify and understand longer-term outcomes after myocarditis occurring after COVID-19 vaccination (279).
- 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. PRAC assessment is ongoing

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 (280).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 (281).

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. 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) (282).

On the 29 October, FDA authorized Pfizer-BioNTech COVID-19 Vaccine Comirnaty® for emergency use in children 5 through 11 years of age, and since early November, vaccination of this age group is

	recommended in the US. For Europe, EMA is currently evaluating this extended use of Comirnaty® in 5 to 11 year olds and is evaluating use of Spikevax® in children aged 6 to 11.
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** (283). 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 (284,285). Transmission may also occur **indirectly through contaminated surfaces or fomites**, although that risk is generally considered to be low (286). Several studies have shown extensive contamination of inanimate surfaces around an infected person (287) and other respiratory illnesses and coronaviruses can spread through indirect contact (122). 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 (288,289). 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 (286,290). 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 (291–293). Especially in faeces, viral RNA seems to be present later and persists longer than in samples from the upper respiratory tract (294). **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 (291,295,296) but no cases of faeco-oral transmission have been documented (290). 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 (297). 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 (298). 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 (299) and unclear in another (300). In the third study (301), 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 (302,303) and previous experience with SARS (304–306). 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) (307), in fitness centres during Zumba classes (308), during a choir rehearsal (309), in a restaurant without fresh air supply but air being recirculated by the air conditioning (310) or among Chinese bus passengers (311). 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 (312). For the potential of intrauterine **mother-to-child transmission**, see section 'Pregnancy'.

Incubation period *Last update 20 September 2021*	The **mean incubation period** (the period between infection and onset of symptoms) is about 4-6 days with about 95% of individuals developing symptoms within 14 days from infection (313–315). Larger studies and meta-analyses have since been carried out, and confirm a median incubation period ranging between 5 and 6 days (316,317). In a study by Yang *et a*l 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)(316). 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) (318). 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 (319). A rapid review of 40 studies found a median serial interval ranging from 1.0 to 6.0 days (based on 15 estimates) (320) and a meta-analysis of 11 studies calculated a pooled estimate of 5.4 days (321). 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 (322). 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 (323). 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 (324). 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 (323), *Zhang et al*. observed a mean serial interval of 2.3 days (95%CI: 1.4-3.3) for the same outbreak (324). 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 (325). Finally, *Zhang et al*. observed a **generation time** of 2.9 days (95%CI: 2.4-3.3) (324). 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 (326).
Contagious period *Last update 8 September 2021*	**Beginning of contagious period:** Viral load in the upper respiratory tract is highest around the day of symptom onset, followed by a gradual decline over time (327–334). 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 (335). 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 (307,336–338). 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 (339). Throughout the epidemic, evidence of pre-symptomatic transmission has accumulated (330,336,339–342). 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 (343). 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 (333). 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 (344). In South Korea, a large outbreak occurred among fitness instructors and attendees where the index patient developed symptoms only 3 days after the workshop (308).

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 (345). 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 (346). 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 (344). 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 (319).

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 (347).

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 (348).

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 (349)

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%]) (336). 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 (350). Since then, the study with the largest sample size that has been published is by Singanayagam et al (351). 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. **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 (352,353) and hence might be less infectious (354,355). 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 (356–359). 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 (211,360–362). 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 (211,363,364). This was also observed in a prospective observational study in the UK, published in the Lancet Infectious Diseases (240). 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 (361), 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) (363). 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 (319,365–370), including pregnant women (371) and nursing home residents (372). The reported proportions of asymptomatic infections have varied widely, from 17.9% (366) to well over 60% (373). These differences are most likely due to incomplete symptom assessment and lack of follow-up (374) 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** (375). Another review, including only 13 studies at low risk of bias, concluded that 17% of cases remain asymptomatic (14-20%) (376). 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 (377) as well as in various other studies (376,378,379). 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 (374,380). 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 (381). 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 (319,328).

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 (315). Other symptoms included fatigue (23%), myalgia (15%), and gastrointestinal symptoms (+-8%) (382). 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 (383). 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) (384–387). 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 (388,389). Notably, anosmia has been reported after infection with other respiratory or coronaviruses (390). 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) (391). Data from more than 72,000 cases from China classified **cases as mild (81%), severe (14%), or critical (5%)** (392). 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 (393). Other symptoms that appear more frequent in COVID-19 in comparison to other respiratory infections are fever, myalgia and general malaise/fatigue (394–397). 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.) (398,399). 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 (400), only few case reports are found in the scientific literature (401,402) 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** (403,404) and a high rate of **cardiovascular complications** (387). 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) (405). In a double-center study in the Netherlands, a 31% incidence of thrombotic complications in ICU patients with COVID-19 infections is reported (406). 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% (106). In Wuhan, in admitted patients, mortality reached 25% in the middle of the epidemic (382). On March 22, the CFR in the oldest age group (>80y) in Italy was 23% (407). 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% (408). 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 (409). 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. (410) The overall infection fatality risk was 1.1-1.4% in men and 0.6-0.8% in women, which is higher than for e.g. Influenza. There was a marked difference by age and sex, ranging from 0.01% in girls 0-9y old to 16.4% in men aged 80 years and older. 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** (411,412). 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 (413). The **pathophysiology is not yet fully understood** and consists probably of multiple, intertwined mechanisms (414,415). Two categories of mechanisms are distinguished (413,415): (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** (413,415–417). Post-COVID conditions not only appear in patients that have been severely ill but even in patients that remained asymptomatic (412). 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 (418). 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 (417,419). 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 (420). For more information on long-COVID in children, see section children. **Many different organs are affected, in particular heart, lungs and brain** (413). 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. (413,415,419,421,422). 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 (423–428). 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) (429–432). 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 (433). 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 (414,415). 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 (434). ECDC therefore expects post-COVID to create a high burden, with additional pressures on the health care system (435). There is no simple test for **diagnosing** long COVID (413). 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 (436). Further studies are necessary to know how to **follow-up** COVID-19 patients but also to prevent these long-term consequences (437). A multidisciplinary, multispecialty approach will most probably be required (413,438). 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 (439). 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 (439). Persistence of **high viral loads** has been associated with disease severity (440). 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 (441). 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 (442). 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 (443). 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 (444). 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) (442). 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 (445). **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 (382,398,446,447). 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 (382). 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 (447). 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 (448). An additional mechanism of disease pathogenesis hypothesized by several authors is **antibody-dependent enhancement** (ADE) (449,450). 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 (451). 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 (452–455). Longitudinal follow-up of COVID-19 patients has shown that antibody levels may rapidly wane, declining within 2 months after symptom onset (453,454) but thereafter remain relatively stable for 6-12 months (456–458). 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) (452). 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 (456,458,459).

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 (460,461). 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 (462). 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 (463). In this study and others, the magnitude of the nAb response, as for total antibody levels, correlated with disease severity (452,463). 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 (452).

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 (464,465). 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 (466). 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 (467).

Cellular response: Various studies have shown that virus-specific T cell responses can be detected in convalescent COVID-19 patients (468–477), even in seronegative patients indicating that immunity can be maintained even in absence of circulating antibodies (468,472,473,478). 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 (468,469,471,479).

Looking at the T-cell subsets, CD4+ responses were established in >90 % of convalescent patients and CD8+ responses in 70% of the cases (475).

Using different SARS-CoV-2 epitopes, it was shown that the strongest T-cells responses were against the spike protein (474,475), but also responses against membrane, nucleocapsid, env and ORFs were observed (468–470,473–475). Although not observed in all studies (469,480), it is interesting that in several studies T cell reactivity to SARS-CoV-2 epitopes was detected in 20-60% of healthy individuals (468,470,474–476), 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 (481). 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 (482). 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 (473,474,482,483). 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 (484). **Memory B-cells** also accumulate over the first months after SARS-COV-2 infection allowing for new antibodies production upon reinfection (485). Antibodies expressed by memory B-cell have somatic hypermutations leading to potentially increased potency (486). **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 (485). Although antibodies are usually a reasonable correlate of antiviral immunity, it is important to note that data so far does not allow to affirm that the detection of SARS-CoV-2 antibodies indicates immunity to subsequent infection (carriage or disease). Recent studies suggest however that neutralising antibodies are good correlates of vaccine induced immunity (487). **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 03 September 2021*	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 (488). 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 (491,494). When the viruses from two episodes are associated to different clades or lineages, the evidence of reinfection is stronger (488,490,492). **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 (495). 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) (496). 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 (456). 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 (497). Higher IgG levels have been associated with severe disease, but even mild disease seems to offer good protection for at least 6-8 months (456,457,498). **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 (499). 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 (500). 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 (457,498,501) or retrospective designs using population-wide data (497,502–504), 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 (196) (see also section genetic diversity and variants). **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 (501). **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 (505). One study even described a positive PCR result 104 days after the first positive test in an obstetric patient (506). 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 (507). 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 (507–509), 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) (510). 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 (510). 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 (511). 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 (512).
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 (382). 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 (513).
RT-PCR *Last update* *17 November 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. • **Timing and type of specimen:** the overall quality of studies assessing sensitivity of PCR is low: different definitions are used (eg. 'pharyngeal' has been used to refer to both naso-pharyngeal and oro-pharyngeal samples, 'nasal' for either naso-pharyngeal or anterior nares), timing of testing with regards to symptoms are not always addressed, reference used for sensitivity calculation not specified, primers and probes used for assay not described etc. Nevertheless, important information has been obtained. **With regards to timing of testing and impact on sensitivity:** In a literature review and pooled analysis, Kucirka *et al* analyzed the rate of false negative RT-PCR on upper respiratory tract samples of COVID-19 symptomatic patients (in- & out-patients) in relation to the number of days since exposure (514). 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 (515). **With regards to sample type:** Sensitivity of RT-PCR appears to be higher for lower respiratory samples than for upper respiratory tract samples (291,327,516). 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 (328–331). RT-PCR may remain positive longer in lower respiratory samples (327,516). In a prospective cohort of 67 COVID-19 pneumonia cases (Chongqing, China), median duration of SARS-CoV-2 RNA shedding was 12 days (3-38 days) in nasopharyngeal swab versus 19 days (5-37 days) in sputum. In this study, prolonged viral shedding was also observed in severe patients compared to non-severe patients (516). 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%) (517). Sensitivity of RT-PCR on oral fluid samples is dicussed further in the document. • **Sampling technique and pre-analytical precautions**: correct sample collection technique is essential to ensure best test performance and avoid false-negatives. Guidance is available in Fr and Dutch. Correct swabs (preferably flocked), transport medium (Universal Transport Medium) and transport precautions to laboratory (ideally immediately after sample collection) must be applied. • **Test kit quality**: several studies have been published comparing SARS-CoV-2 detection assays (518,519), 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%) (520). With the exception of SARS-CoV, no cross-reactivity is found when tested against a large panel of microorganisms including the common human coronaviruses (521). 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 (522), but their cost is higher.
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 (523). 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 (524). Reduction in the circulation of other seasonal respiratory viruses during the first peak of the epidemic was also observed in several regions worldwide (525–527). 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 (528). 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 (529,530). Some studies observed more extended cases of co-infections with bacterial pathogens (531).

	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 (532). 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 (533,534). Their specificity is similar to that of an RT-PCR, but their sensitivity is slightly lower (535).
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 (517,536–542). 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) (543). 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) (544). 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 (545). 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 (546). 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 (548). 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 (549). 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) (550). 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 (551–553). 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 (554). 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.
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 (555). 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 (556). Inversely, negative Chest CT in PCR positive patients has also been reported (557), 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 (558). 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 (559). 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 (370). Similarly, on the "Diamond Princess cruise ship", 41 out of 76 asymptomatic cases (54%) had abnormal CT findings (560). **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) (561) 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 (455,562)

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 (563).

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) (564). 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 %) (565). An evaluation of COVID 19 serological assays found sensitivities ranging from 81 to 99 % and specificities ranging from 94 to 99 % (564).

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) (566). Inversely, cross-reactivity has been found when sera from SARS-CoV-2 patients are tested using SARS-CoV serological assays (567). 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 (568) 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 (569).
Rapid Ag and Ab tests *Last update 22 September June 2020*	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 (570). Some later developed tests show, however, better performance with overall sensitivities of around 70% (571,572). 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 (573). 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%)(574). 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 (575). 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 (572). In Germany, 96 of the 122 evaluated tests met the sensitivity limit of 75% with Ct<=25 (576). 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 (577–583) and some showed very disappointing results with regard to the sensitivity of rapid Ag tests on saliva (579,581–583). 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 (581). **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 (584,585).

	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% (586). 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%) (587). Positive results require a seroconversion, therefore these tests are not useful for early COVID-19 diagnosis or in the early stage of the disease (see section "serology", in particular 'timing to seroconversion'). As currently the correlation between antibody (levels) and protection against reinfection or disease is currently unknown, a positive test result can only inform of a past infection. This will have to be taken into consideration when deciding on the clinical application of such tests, which has not yet been clearly defined. Over 220 commercial rapid test kits have been developed from 20 countries, of variable performance (587). As with the other in vitro diagnostic medical devices developed for COVID-19 diagnosis, all rapid tests should be registered and quality checked by the usual regulatory bodies.
Repetitive testing *Last update 5 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 (588–590). Most studies recommend a periodicity of at least 2-3 times a week (591–594), but others state that relatively infrequent testing, such as every one or two weeks, is already sufficient to keep controlled outbreaks small (595). 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 (596). Models also show that the health benefits of repeated testing with a rapid antigen test far exceed their costs (597). 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 (598,599). 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 (600).
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 (601,602).
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 • Our World in Data: Coronavirus Pandemic (COVID-19) - Statistics and Research - Our World in Data
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 (603) 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) (604). 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 (605). 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) (606).
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 (607–609). 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 (610,611). Moreover, certain studies have considered meteorological parameters only, without correcting for other parameters impacting disease dynamics, such as population density, population age distribution, etc (612). 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 (613). 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 (614). 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]) (615). 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 (616). 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 (617).
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 (618). **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%) (392). 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) (382). 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 (619). 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 (409). 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 (620). **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 (621). 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%) (622).

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) (619). 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 (382).

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) (623).

Although less common, some studies documented an association between neurologic disorders and severe COVID-19 (624–627).

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 (392). In the Lombardy (Italy) outbreak, a large retrospective case-series on 1591 COVID-19 patients admitted to ICU, 82% were male (408). 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 (382). 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 (619). 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 (625,628–630). 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) (631). 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 (632,633).

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 (382). 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 (634).

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 (635).

Obesity: Obesity has emerged as an independent risk factor for susceptibility to and severity of COVID-19 (628,636). 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) (637)

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]) (638). 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 (639). 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) (640). 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 (641,642). 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 (643). 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** (644). 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). (645) 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. (646) 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. (647) 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. (648) 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 (649–653). 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 (654–658). Mathematical modelling concluded that children are about half as likely to get infected as adults (654), a conclusion that was supported by a meta-analysis of contact tracing data by Viner et al (658). 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 (659). Several mechanisms have been proposed to explain this relative resistance, from immune imprinting by other viruses (660) to distribution, maturation, and functioning of viral receptors (661). 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 (662), 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 (663). A Belgian seroprevalence study in schools showed comparable infection rates in children, teachers and the general population by end of May 2021 (664).

The role of children in the transmission dynamics of SARS-CoV-2 remains much debated (665) **although there exists a consensus that young children are not the drivers of transmission** (666). 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 (667). 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 (668). 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 (669). 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) (670,671) and children rarely cause secondary cases (672,673). A 'lower risk of onwards transmission' is however not zero risk: transmission has been described from day care settings in Poland (674) and the US (675). 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 (676).

Data on **transmission in school settings** is increasing. Contact tracing and cluster investigations in schools before lockdown done in Ireland (677), France (678,679) and New South Wales (680) 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 (681). 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 (682). 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 (682–686). 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 (687,688). 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 (689) 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 (690). 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 (691). 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 to 11 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 (691–696). Specialized care is required but survival is high (654). A higher proportion is noticed in African and Hispanic children (654).
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 (697). However, preliminary data from small case series, reported similar clinical characteristics in pregnant women as in the general population (698–703). These findings were then confirmed in obstetric surveillance data from the UK (704) and a prospective cohort from NYC (705). 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 (706). 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 (707). 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 (708). 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 (709). 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 (710) **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 (711). **Risk to the fetus:** In utero transmission is possible, as proven by a case from France (712). 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** (712–715). 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 (713). 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 (716,717). Pre-term and cesarean delivery rates seem related to geographical differences rather than being a result of COVID-19 (718). Some authors have warned for the possibility of intrauterine growth restriction (699), a concern that is strengthened by the findings of increased vasculopathy in placentas from mothers with SARS-CoV-2 (714,719). **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 (715,720).
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 (721,722). 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 (723–728). Similar conclusions are drawn from later matched case-control studies comparing HIV and non-HIV patients, albeit limited in size (729,730). 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 (731). 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 (732). 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 (733). 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 (734).

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 (735).

Importantly, although mild presentation and recovery from COVID-19 severe disease has been described in severely immunocompromised PLHIV (724,727), 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 (736,737).

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 (738–741). Most frequent cancer types reported among COVID-19 hospitalized patients are lung, breast, gastrointestinal, genitourinary, prostate and hematological (742–747). Case-fatality rate (CFR) in cancer patients with COVID-19 ranges between 11% to 32% (742–748). 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%) (744,748). Among solid cancer patients, patients with lung cancer have been shown

	to have the highest death rate and highest frequency of severe events (747). 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%) (749). 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 (740,746). Two larger studies on COVID-19 in patients with **hematological malignancies** have been conducted (750,751). 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 (750). 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 (745–748,752). On the other hand, Yang et al. describes chemotherapy as a risk factor for in-hospital death (744). Receiving radiotherapy was also suggested to be associated with increased mortality (753). The study from Dai et al. suggests that patients with surgery or immunotherapy have a higher death rate (747). 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 (754,755). 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] (756). A larger international survey documented disease course and outcome of 1046 COVID-19 patients with DS (757). 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 (758).
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 (759,760). An RCT found no impact of ACEi/ARB switch in COVID-19 (761). 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 (762). 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).

References

1. Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020 Mar;579(7798):270–3.

2. Adnan Shereen M, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: origin, transmission, and characteristics of human coronaviruses. Journal of Advanced Research [Internet]. 2020 Mar 16 [cited 2020 Mar 29]; Available from: http://www.sciencedirect.com/science/article/pii/S2090123220300540

3. Fehr AR, Perlman S. Coronaviruses: An Overview of Their Replication and Pathogenesis. Coronaviruses. 2015 Feb 12;1282:1–23.

4. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020 Apr 16;181(2):271-280.e8.

5. [cited 2021 Feb 15]. Available from: https://mendel.bii.a-star.edu.sg/METHODS/corona/current/MUTATIONS/hCoV-19_Human_2019_WuhanWIV04/hCoV-19_Spike_new_mutations_table.html

6. Korber B, Fischer WM, Gnanakaran S, Yoon H, Theiler J, Abfalterer W, et al. Tracking Changes in SARS-CoV-2 Spike: Evidence that D614G Increases Infectivity of the COVID-19 Virus. Cell. 2020 Aug 20;182(4):812-827.e19.

7. Grubaugh ND, Hanage WP, Rasmussen AL. Making Sense of Mutation: What D614G Means for the COVID-19 Pandemic Remains Unclear. Cell. 2020 Aug;182(4):794–5.

8. Long SW, Olsen RJ, Christensen PA, Bernard DW, Davis JJ, Shukla M, et al. Molecular Architecture of Early Dissemination and Massive Second Wave of the SARS-CoV-2 Virus in a Major Metropolitan Area. medRxiv. 2020 Sep 29;2020.09.22.20199125.

9. Volz EM, Hill V, McCrone JT, Price A, Jorgensen D, O'Toole A, et al. Evaluating the effects of SARS-CoV-2 Spike mutation D614G on transmissibility and pathogenicity. medRxiv. 2020 Sep 1;2020.07.31.20166082.

10. Hou YJ, Chiba S, Halfmann P, Ehre C, Kuroda M, Dinnon KH, et al. SARS-CoV-2 D614G variant exhibits efficient replication ex vivo and transmission in vivo. Science. 2020 Dec 18;370(6523):1464–8.

11. Dearlove B, Lewitus E, Bai H, Li Y, Reeves DB, Joyce MG, et al. A SARS-CoV-2 vaccine candidate would likely match all currently circulating variants. PNAS [Internet]. 2020 Aug 31 [cited 2020 Sep 7]; Available from: https://www.pnas.org/content/early/2020/08/28/2008281117

12. Mahase E. Covid-19: What have we learnt about the new variant in the UK? BMJ. 2020 Dec 23;371:m4944.

13. Threat Assessment Brief: Rapid increase of a SARS-CoV-2 variant with multiple spike protein mutations observed in the United Kingdom [Internet]. European Centre for Disease Prevention and Control. 2020 [cited 2020 Dec 24]. Available from: https://www.ecdc.europa.eu/en/publications-data/threat-assessment-brief-rapid-increase-sars-cov-2-variant-united-kingdom

14. NERVTAG meeting on SARS-CoV-2 variant under investigation VUI-202012/01.pdf [Internet]. [cited 2020 Dec 24]. Available from: https://khub.net/documents/135939561/338928724/SARS-CoV-2+variant+under+investigation%2C+meeting+minutes.pdf/962e866b-161f-2fd5-1030-32b6ab467896?t=1608491166921

15. Davies, Nicholas G. Estimated transmissibility and severity of novel SARS-CoV-2 Variant of Concern 202012/01 in England.

16. Lineage-specific growth of SARS-CoV-2 B.1.1.7 during the English national lockdown - SARS-CoV-2 coronavirus / nCoV-2019 Genomic Epidemiology [Internet]. Virological. 2020 [cited 2021 Jan 29]. Available from: https://virological.org/t/lineage-specific-growth-of-sars-cov-2-b-1-1-7-during-the-english-national-lockdown/575

17. Leung K, Shum MH, Leung GM, Lam TT, Wu JT. Early transmissibility assessment of the N501Y mutant strains of SARS-CoV-2 in the United Kingdom, October to November 2020. Eurosurveillance. 2021 Jan 7;26(1):2002106.

18. Risk related to the spread of new SARS-CoV-2 variants of concern in the EU/EEA – first update [Internet]. European Centre for Disease Prevention and Control. 2021 [cited 2021 Jan 29]. Available from: https://www.ecdc.europa.eu/en/publications-data/covid-19-risk-assessment-spread-new-variants-concern-eueea-first-update

19. Buchan SA, Tibebu S, Daneman N, Whelan M, Vanniyasingam T, Murti M, et al. Increased household secondary attacks rates with Variant of Concern SARS-CoV-2 index cases. Clin Infect Dis. 2021 Jun 9;ciab496.

20. Curran J, Dol J, Boulos L, Somerville M, McCulloch H, MacDonald M, et al. Transmission characteristics of SARS-CoV-2 variants of concern Rapid Scoping Review. medRxiv. 2021 Apr 25;2021.04.23.21255515.

21. Technical_Briefing_VOC_SH_NJL2_SH2.pdf [Internet]. [cited 2021 Feb 5]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/947048/Technical_Briefing_VOC_SH_NJL2_SH2.pdf

22. Investigation of novel SARS-CoV-2 variant: Variant of Concern 202012/01 [Internet]. GOV.UK. [cited 2021 Jan 12]. Available from: https://www.gov.uk/government/publications/investigation-of-novel-sars-cov-2-variant-variant-of-concern-20201201

23. Technical_Briefing_VOC202012-2_Briefing_2_FINAL.pdf [Internet]. [cited 2021 Jan 29]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/949639/Technical_Briefing_VOC202012-2_Briefing_2_FINAL.pdf

24. S1095_NERVTAG_update_note_on_B.1.1.7_severity_20210211.pdf [Internet]. [cited 2021 Apr 9]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/961042/S1095_NERVTAG_update_note_on_B.1.1.7_severity_20210211.pdf

25. Funk T, Pharris A, Spiteri G, Bundle N, Melidou A, Carr M, et al. Characteristics of SARS-CoV-2 variants of concern B.1.1.7, B.1.351 or P.1: data from seven EU/EEA countries, weeks 38/2020 to 10/2021. Eurosurveillance [Internet]. 2021 Apr 22 [cited 2021 May 3];26(16). Available from: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2021.26.16.2100348

26. Investigation of novel SARS-CoV-2 variant: Variant of Concern 202012/01. :19.

27. PANGO lineages [Internet]. [cited 2021 Apr 9]. Available from: https://cov-lineages.org/global_report_B.1.1.7.html

28. Genomic surveillance of SARS-CoV-2 in Belgium [Internet]. [cited 2021 Apr 9]. Available from: https://www.uzleuven.be/nl/laboratoriumgeneeskunde/genomic-surveillance-sars-cov-2-belgium

29. Wise J. Covid-19: The E484K mutation and the risks it poses. BMJ. 2021 Feb 5;372:n359.

30. Tegally H, Wilkinson E, Giovanetti M, Iranzadeh A, Fonseca V, Giandhari J, et al. Detection of a SARS-CoV-2 variant of concern in South Africa. Nature. 2021 Apr;592(7854):438–43.

31. 2021_01_11_Transmissibility_and_severity_of_501Y_V2_in_SA.pdf [Internet]. [cited 2021 Jan 29]. Available from: https://cmmid.github.io/topics/covid19/reports/sa-novel-variant/2021_01_11_Transmissibility_and_severity_of_501Y_V2_in_SA.pdf

32. Wibmer CK, Ayres F, Hermanus T, Madzivhandila M, Kgagudi P, Lambson BE, et al. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. bioRxiv. 2021 Jan 19;2021.01.18.427166.

33. Cele S, Gazy I, Jackson L, Hwa S-H, Tegally H, Lustig G, et al. Escape of SARS-CoV-2 501Y.V2 variants from neutralization by convalescent plasma. medRxiv. 2021 Jan 26;2021.01.26.21250224.

34. Naveca F, Nascimento V, Souza V, Corado A. Phylogenetic relationship of SARS-CoV-2 sequences from Amazonas with emerging Brazilian variants harboring mutations E484K and N501Y in the Spike protein - SARS-CoV-2 coronavirus / nCoV-2019 Genomic Epidemiology [Internet]. Virological. 2021 [cited 2021 Jun 30]. Available from: https://virological.org/t/phylogenetic-relationship-of-sars-cov-2-sequences-from-amazonas-with-emerging-brazilian-variants-harboring-mutations-e484k-and-n501y-in-the-spike-protein/585

35. Genomic characterisation of an emergent SARS-CoV-2 lineage in Manaus: preliminary findings - SARS-CoV-2 coronavirus / nCoV-2019 Genomic Epidemiology [Internet]. Virological. 2021 [cited 2021 Jan 29]. Available from: https://virological.org/t/genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-manaus-preliminary-findings/586

36. Coutinho RM, Marquitti FMD, Ferreira LS, Borges ME, Silva RLP da, Canton O, et al. Model-based estimation of transmissibility and reinfection of SARS-CoV-2 P.1 variant. medRxiv. 2021 Mar 23;2021.03.03.21252706.

37. Faria NR, Mellan TA, Whittaker C, Claro IM, Candido D da S, Mishra S, et al. Genomics and epidemiology of a novel SARS-CoV-2 lineage in Manaus, Brazil. medRxiv. 2021 Mar 3;2021.02.26.21252554.

38. Cherian S, Potdar V, Jadhav S, Yadav P, Gupta N, Das M, et al. Convergent evolution of SARS-CoV-2 spike mutations, L452R, E484Q and P681R, in the second wave of COVID-19 in Maharashtra, India. bioRxiv. 2021 May 3;2021.04.22.440932.

39. SARS-CoV-2 variants of concern and variants under investigation [Internet]. Public Health England; p. 77. (Technical briefing). Report No.: 15. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/993879/Variants_of_Concern_VOC_Technical_Briefing_15.pdf

40. 25_June_2021_Risk_assessment_for_SARS-CoV-2_variant_DELTA.pdf [Internet]. [cited 2021 Jun 30]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/996699/25_June_2021_Risk_assessment_for_SARS-CoV-2_variant_DELTA.pdf

41. Threat Assessment Brief: Implications for the EU/EEA on the spread of the SARS-CoV-2 Delta (B.1.617.2) variant of concern [Internet]. European Centre for Disease Prevention and Control. 2021 [cited 2021 Jul 2]. Available from: https://www.ecdc.europa.eu/en/publications-data/threat-assessment-emergence-and-impact-sars-cov-2-delta-variant

42. Campbell F, Archer B, Laurenson-Schafer H, Jinnai Y, Konings F, Batra N, et al. Increased transmissibility and global spread of SARS-CoV-2 variants of concern as at June 2021. Eurosurveillance. 2021 Jun 17;26(24):2100509.

43. Twohig KA, Nyberg T, Zaidi A, Thelwall S, Sinnathamby MA, Aliabadi S, et al. Hospital admission and emergency care attendance risk for SARS-CoV-2 delta (B.1.617.2) compared with alpha (B.1.1.7) variants of concern: a cohort study. Lancet Infect Dis. 2021 Aug 27;S1473-3099(21)00475-8.

44. Pango lineages [Internet]. Available from: https://cov-lineages.org/lineage_list.html

45. SARS-CoV-2 variants of concern and variants under investigation in England Technical briefing 26. :31.

46. SARS-CoV-2 variants of concern and variants under investigation in England - Technical briefing 28. :52.

47. 10 November 2021 Risk assessment for SARS-CoV-2 variant: VUI-21OCT-01 AY.4.2. :1.

48. New COVID-19 variant detected in South Africa [Internet]. NICD. 2021 [cited 2021 Nov 26]. Available from: https://www.nicd.ac.za/new-covid-19-variant-detected-in-south-africa/

49. B.1.1 decendant associated with Southern Africa with high number of Spike mutations · Issue #343 · cov-lineages/pango-designation [Internet]. GitHub. [cited 2021 Nov 26]. Available from: https://github.com/cov-lineages/pango-designation/issues/343

50. Africa Centres for Disease Control and Prevention's Statement regarding the new SARS-COV-2 virus variant B.1.1.529 [Internet]. Africa CDC. [cited 2021 Nov 26]. Available from: https://africacdc.org/news-item/africa-centres-for-disease-control-and-preventions-statement-regarding-the-new-sars-cov-2-virus-variant-b-1-1-529/

51. Israel detects its first case of new, highly mutated COVID-19 strain | The Times of Israel [Internet]. [cited 2021 Nov 26]. Available from: https://www.timesofisrael.com/israel-detects-first-case-of-new-highly-mutated-covid-19-strain/

52. Implications of the emergence and spread of the SARS-CoV-2 B.1.1.529 variant of concern (Omicron) for the EU/EEA. :7.

53. Classification of Omicron (B.1.1.529): SARS-CoV-2 Variant of Concern [Internet]. [cited 2021 Nov 27]. Available from: https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern

54. Deng X, Garcia-Knight MA, Khalid MM, Servellita V, Wang C, Morris MK, et al. Transmission, infectivity, and antibody neutralization of an emerging SARS-CoV-2 variant in California carrying a L452R spike protein mutation. medRxiv. 2021 Mar 9;2021.03.07.21252647.

55. McCallum M, Bassi J, De Marco A, Chen A, Walls AC, Di Iulio J, et al. SARS-CoV-2 immune evasion by the B.1.427/B.1.429 variant of concern. Science. 2021 Jul 1;eabi7994.

56. CDC. Coronavirus Disease 2019 (COVID-19) [Internet]. Centers for Disease Control and Prevention. 2020 [cited 2021 Jul 2]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html

57. Laiton-Donato K, Franco-Muñoz C, Álvarez-Díaz DA, Ruiz-Moreno HA, Usme-Ciro JA, Prada DA, et al. Characterization of the emerging B.1.621 variant of interest of SARS-CoV-2. medRxiv. 2021 May 10;2021.05.08.21256619.

58. genomic_surveillance_update_210831.pdf [Internet]. [cited 2021 Sep 1]. Available from: https://assets.uzleuven.be/files/2021-09/genomic_surveillance_update_210831.pdf

59. Malik YS, Sircar S, Bhat S, Sharun K, Dhama K, Dadar M, et al. Emerging novel coronavirus (2019-nCoV)-current scenario, evolutionary perspective based on genome analysis and recent developments. Vet Q. 2020 Dec;40(1):68–76.

60. Wu F, Zhao S, Yu B, Chen Y-M, Wang W, Song Z-G, et al. A new coronavirus associated with human respiratory disease in China. Nature [Internet]. 2020 Feb 3 [cited 2020 Feb 5]; Available from: http://www.nature.com/articles/s41586-020-2008-3

61. Latinne A, Hu B, Olival KJ, Zhu G, Zhang L, Li H, et al. Origin and cross-species transmission of bat coronaviruses in China. bioRxiv [Internet]. 2020 May 31 [cited 2020 Sep 4]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7302205/

62. Guo Y-R, Cao Q-D, Hong Z-S, Tan Y-Y, Chen S-D, Jin H-J, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status. Military Medical Research. 2020 Mar 13;7(1):11.

63. Liu Z, Xiao X, Wei X, Li J, Yang J, Tan H, et al. Composition and divergence of coronavirus spike proteins and host ACE2 receptors predict potential intermediate hosts of SARS-CoV-2. J Med Virol. 2020 Feb 26;

64. Luan J, Lu Y, Jin X, Zhang L. Spike protein recognition of mammalian ACE2 predicts the host range and an optimized ACE2 for SARS-CoV-2 infection. Biochemical and Biophysical Research Communications [Internet]. 2020 Mar 19 [cited 2020 Mar 25]; Available from: http://www.sciencedirect.com/science/article/pii/S0006291X2030526X

65. Qiu Y, Zhao Y-B, Wang Q, Li J-Y, Zhou Z-J, Liao C-H, et al. Predicting the angiotensin converting enzyme 2 (ACE2) utilizing capability as the receptor of SARS-CoV-2. Microbes and Infection [Internet]. 2020 Mar 19 [cited 2020 Mar 24]; Available from: http://www.sciencedirect.com/science/article/pii/S1286457920300496

66. Koopmans M. SARS-CoV-2 and the human-animal interface: outbreaks on mink farms. The Lancet Infectious Diseases [Internet]. 2020 Nov 20 [cited 2020 Dec 14];0(0). Available from: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30912-9/abstract

67. Mink-cluster-5-short-report_AFO2.pdf [Internet]. [cited 2020 Dec 14]. Available from: https://files.ssi.dk/Mink-cluster-5-short-report_AFO2

68. Munnink BBO, Sikkema RS, Nieuwenhuijse DF, Molenaar RJ, Munger E, Molenkamp R, et al. Transmission of SARS-CoV-2 on mink farms between humans and mink and back to humans.

Science [Internet]. 2020 Nov 10 [cited 2020 Dec 14]; Available from: https://science.sciencemag.org/content/early/2020/11/09/science.abe5901

69. Doremalen N van, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. New England Journal of Medicine [Internet]. 2020 Mar 17 [cited 2020 Mar 19]; Available from: https://www.nejm.org/doi/10.1056/NEJMc2004973

70. Chin AWH, Chu JTS, Perera MRA, Hui KPY, Yen H-L, Chan MCW, et al. Stability of SARS-CoV-2 in different environmental conditions. The Lancet Microbe. 2020 May 1;1(1):e10.

71. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. Features, Evaluation and Treatment Coronavirus (COVID-19). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 [cited 2020 Mar 23]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK554776/

72. Hergebruik mondmaskers en isolatiekleding | RIVM [Internet]. [cited 2020 Apr 8]. Available from: https://www.rivm.nl/documenten/hergebruik-mondmaskers-isolatiekleding

73. FDA. Battelle Decontamination System - Letter of Authorization [Internet]. [cited 2020 Apr 8]. Available from: https://www.fda.gov/media/136529/download

74. RKI - Coronavirus SARS-CoV-2 - Hinweise zur Verwendung von Masken (MNS-, FFP- sowie Mund-Nasen-Bedeckung) (2.4.2020) [Internet]. [cited 2020 Apr 8]. Available from: https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Arbeitsschutz_Tab.html?nn=13490888

75. World Health Organization. Rational use of personal protective equipment for coronavirus disease (COVID-19) and considerations during severe shortages [Internet]. 6th April [cited 2020 Apr 17]. Available from: https://apps.who.int/iris/bitstream/handle/10665/331695/WHO-2019-nCov-IPC_PPE_use-2020.3-eng.pdf

76. Xie X, Li Y, Chwang ATY, Ho PL, Seto WH. How far droplets can move in indoor environments--revisiting the Wells evaporation-falling curve. Indoor Air. 2007 Jun;17(3):211–25.

77. Chu DK, Akl EA, Duda S, Solo K, Yaacoub S, Schünemann HJ, et al. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. The Lancet [Internet]. 2020 Jun 1 [cited 2020 Jun 2];0(0). Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31142-9/abstract

78. Johnson GR, Morawska L, Ristovski ZD, Hargreaves M, Mengersen K, Chao CYH, et al. Modality of human expired aerosol size distributions. Journal of Aerosol Science. 42(12):839–51.

79. Sande M van der, Teunis P, Sabel R. Professional and Home-Made Face Masks Reduce Exposure to Respiratory Infections among the General Population. PLOS ONE. 2008 Jul 9;3(7):e2618.

80. Dato VM, Hostler D, Hahn ME. Simple Respiratory Mask. Emerg Infect Dis. 2006 Jun;12(6):1033–4.

81. Davies A, Thompson K-A, Giri K, Kafatos G, Walker J, Bennett A. Testing the Efficacy of Homemade Masks: Would They Protect in an Influenza Pandemic? Disaster Med Public Health Prep. 2013 May 22;7(4):413–8.

82. Chughtai AA, Seale H, MacIntyre CR. Use of cloth masks in the practice of infection control – evidence and policy gaps. Int j infect control [Internet]. 2013 Jun 19 [cited 2020 Apr 15];9(3). Available from: http://www.ijic.info/article/view/11366

83. Anfinrud P, Stadnytskyi V, Bax CE, Bax A. Visualizing Speech-Generated Oral Fluid Droplets with Laser Light Scattering. New England Journal of Medicine. 2020 Apr 15;0(0):null.

84. Fischer EP, Fischer MC, Grass D, Henrion I, Warren WS, Westman E. Low-cost measurement of face mask efficacy for filtering expelled droplets during speech. Science Advances. 2020 Sep 1;6(36):eabd3083.

85. Ueki H, Furusawa Y, Iwatsuki-Horimoto K, Imai M, Kabata H, Nishimura H, et al. Effectiveness of Face Masks in Preventing Airborne Transmission of SARS-CoV-2. mSphere [Internet]. 2020 Oct 28 [cited 2020 Dec 2];5(5). Available from: https://msphere.asm.org/content/5/5/e00637-20

86. Mathematical Modeling of the Effectiveness of Facemasks in Reducing the Spread of Novel Influenza A (H1N1) [Internet]. [cited 2020 Apr 8]. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0009018

87. Brienen NCJ, Timen A, Wallinga J, van Steenbergen JE, Teunis PFM. The effect of mask use on the spread of influenza during a pandemic. Risk Anal. 2010 Aug;30(8):1210–8.

88. Yan J, Guha S, Hariharan P, Myers M. Modeling the Effectiveness of Respiratory Protective Devices in Reducing Influenza Outbreak. Risk Analysis. 2019 Mar 1;39(3):647–61.

89. Clapp PW, Sickbert-Bennett EE, Samet JM, Berntsen J, Zeman KL, Anderson DJ, et al. Evaluation of Cloth Masks and Modified Procedure Masks as Personal Protective Equipment for the Public During the COVID-19 Pandemic. JAMA Intern Med [Internet]. 2020 Dec 10 [cited 2021 Jan 5]; Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2774266

90. Bundgaard H, Bundgaard JS, Raaschou-Pedersen DET, von Buchwald C, Todsen T, Norsk JB, et al. Effectiveness of Adding a Mask Recommendation to Other Public Health Measures to Prevent SARS-CoV-2 Infection in Danish Mask Wearers. Ann Intern Med [Internet]. 2020 Nov 18 [cited 2020 Dec 2]; Available from: https://www.acpjournals.org/doi/10.7326/M20-6817

91. Ng OT, Marimuthu K, Koh V, Pang J, Linn KZ, Sun J, et al. SARS-CoV-2 seroprevalence and transmission risk factors among high-risk close contacts: a retrospective cohort study. The Lancet Infectious Diseases [Internet]. 2020 Nov 2 [cited 2020 Dec 3]; Available from: http://www.sciencedirect.com/science/article/pii/S1473309920308331

92. Abaluck J, Kwong LH, Styczynski A, Haque A, Kabir A, Bates-Jeffries E, et al. The Impact of Community Masking on COVID-19: A Cluster-Randomized Trial in Bangladesh. :94.

93. BfArM - Empfehlungen des BfArM - Hinweise des BfArM zur Verwendung von selbst hergestellten Masken (sog. „Community-Masken“), medizinischem Mund-Nasen-Schutz (MNS) sowie filtrierenden Halbmasken (FFP2 und FFP3) im Zusammenhang mit dem Coronavirus (SARS-CoV-2 / Covid-19) [Internet]. [cited 2020 Apr 8]. Available from: https://www.bfarm.de/SharedDocs/Risikoinformationen/Medizinprodukte/DE/schutzmasken.html

94. CDC. Coronavirus Disease 2019 (COVID-19) [Internet]. Centers for Disease Control and Prevention. 2020 [cited 2020 Apr 8]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/cloth-face-cover.html

95. Using face masks in the community - Reducing COVID-19 transmission from potentially asymptomatic or pre-symptomatic people through the use of face masks [Internet]. European Centre for Disease Prevention and Control. 2020 [cited 2020 Apr 9]. Available from: https://www.ecdc.europa.eu/en/publications-data/using-face-masks-community-reducing-covid-19-transmission

96. Howard J, Huang A, Li Z, Tufekci Z, Vladimir Z. Face Masks Against COVID-19: An Evidence Review. :8.

97. Cartaud A, Quesque F, Coello Y. Wearing a face mask against Covid-19 results in a reduction of social distancing. PLOS ONE. 2020 Dec 7;15(12):e0243023.

98. World Health Organization,. When and how to use masks [Internet]. 2020 [cited 2020 Jun 5]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public/when-and-how-to-use-masks

99. World Health Organization. Advice on the use of masks for children in the community in the context of COVID-19 [Internet]. 2020 [cited 2020 Nov 6]. Available from: https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-IPC_Masks-Children-2020.1

100. Organization WH. Rational use of personal protective equipment for coronavirus disease (COVID-19): interim guidance, 27 February 2020. 2020 [cited 2020 Mar 24]; Available from: https://apps.who.int/iris/handle/10665/331215

101. Seto W, Tsang D, Yung R, Ching T, Ng T, Ho M, et al. Effectiveness of precautions against droplets and contact in prevention of nosocomial transmission of severe acute respiratory syndrome (SARS). The Lancet. 2003 May 3;361(9368):1519–20.

102. Modes of transmission of virus causing COVID-19: implications for IPC precaution recommendations [Internet]. [cited 2020 Mar 31]. Available from: https://www.who.int/news-room/commentaries/detail/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations

103. Loeb M, Dafoe N, Mahony J, John M, Sarabia A, Glavin V, et al. Surgical Mask vs N95 Respirator for Preventing Influenza Among Health Care Workers: A Randomized Trial. JAMA. 2009 Nov 4;302(17):1865–71.

104. Radonovich LJ, Simberkoff MS, Bessesen MT, Brown AC, Cummings DAT, Gaydos CA, et al. N95 Respirators vs Medical Masks for Preventing Influenza Among Health Care Personnel: A Randomized Clinical Trial. JAMA. 2019 03;322(9):824–33.

105. Long Y, Hu T, Liu L, Chen R, Guo Q, Yang L, et al. Effectiveness of N95 respirators versus surgical masks against influenza: A systematic review and meta-analysis. Journal of Evidence-Based Medicine [Internet]. [cited 2020 Mar 25];n/a(n/a). Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/jebm.12381

106. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) [Internet]. [cited 2020 Mar 24]. Available from: https://www.who.int/publications-detail/report-of-the-who-china-joint-mission-on-coronavirus-disease-2019-(covid-19)

107. Seto WH. Airborne transmission and precautions: facts and myths. Journal of Hospital Infection. 2015 Apr 1;89(4):225–8.

108. Chou R, Dana T, Jungbauer R, Weeks C. Update Alert 4: Masks for Prevention of Respiratory Virus Infections, Including SARS-CoV-2, in Health Care and Community Settings. Ann Intern Med [Internet]. 2020 Dec 29 [cited 2021 Jan 5]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7774035/

109. Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. PLoS ONE. 2012;7(4):e35797.

110. World Health Organization,. WHO | Infection prevention and control of epidemic-and pandemic prone acute respiratory infections in health care [Internet]. WHO. [cited 2020 Mar 26]. Available from: https://www.who.int/csr/bioriskreduction/infection_control/publication/en/

111. Infection_prevention_and_control_guidance_for_pandemic_coronavirus.pdf [Internet]. [cited 2020 Mar 26]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/874316/Infection_prevention_and_control_guidance_for_pandemic_coronavirus.pdf

112. Jespers V. Aerosol-generating procedures [Internet]. Brussels: KCE. Belgian Healthcare Knowledge Centre; 2020 Apr p. 44. Available from: https://kce.fgov.be/sites/default/files/atoms/files/2020-51_COVID_Aerosol%20KCE_FINAL_19052020_3.pdf

113. Escombe AR, Oeser CC, Gilman RH, Navincopa M, Ticona E, Pan W, et al. Natural ventilation for the prevention of airborne contagion. PLoS Med. 2007 Feb;4(2):e68.

114. Melikov AK, Ai ZT, Markov DG. Intermittent occupancy combined with ventilation: An efficient strategy for the reduction of airborne transmission indoors. Sci Total Environ. 2020 Nov 20;744:140908.

115. Dietz L, Horve PF, Coil DA, Fretz M, Eisen JA, Wymelenberg KVD. 2019 Novel Coronavirus (COVID-19) Pandemic: Built Environment Considerations To Reduce Transmission. mSystems [Internet]. 2020 Apr 28 [cited 2020 Sep 5];5(2). Available from: https://msystems.asm.org/content/5/2/e00245-20

116. Morawska L, Cao J. Airborne transmission of SARS-CoV-2: The world should face the reality. Environment International. 2020 Jun 1;139:105730.

117. Stewart EJ, Schoen LJ, Mead K, Olmsted RN, Sekhar C, Vernon W, et al. ASHRAE Position Document on Infectious Aerosols. 2020;24.

118. Heating, ventilation and air conditioning systems in the context of COVID-19. 2020;5.

119. CDC. Guidelines for preventing the transmission of Mycobacterium tuberculosis in health-care facilities. MMWR. 1994;43(13):1–132.

120. HCSP. Réduction du risque de transmission du coronavirus SARS-CoV-2 par la ventilation et gestion des effluents des patients [Internet]. Paris: Haut Conseil de la Santé Publique; 2020 Mar [cited 2020 May 14]. Available from: https://www.hcsp.fr/Explore.cgi/avisrapportsdomaine?clefr=783

121. European Centres for Disease Control. Heating, ventilation and air-conditioning systems in the context of COVID-19: first update [Internet]. Stockholm: ECDC; 2020 Nov [cited 2020 Nov 12]. Available from: https://www.ecdc.europa.eu/en/publications-data/heating-ventilation-air-conditioning-systems-covid-19

122. World Health Organization. Mask use in the context of COVID-19: interim guidance, 1 December 2020 [Internet]. Geneva; 2020 Dec [cited 2020 Dec 8]. Available from: https://apps.who.int/iris/handle/10665/337199

123. Dai H, Zhao B. Association of infected probability of COVID-19 with ventilation rates in confined spaces: a Wells-Riley equation based investigation [Internet]. Emergency Medicine; 2020 Apr [cited 2020 Sep 4]. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.04.21.20072397

124. Buonanno G, Morawska L, Stabile L. Quantitative assessment of the risk of airborne transmission of SARS-CoV-2 infection: prospective and retrospective applications [Internet]. Infectious Diseases (except HIV/AIDS); 2020 Jun [cited 2020 Sep 3]. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.06.01.20118984

125. Entrenas Castillo M, Entrenas Costa LM, Vaquero Barrios JM, Alcalá Díaz JF, López Miranda J, Bouillon R, et al. “Effect of calcifediol treatment and best available therapy versus best available

therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study." The Journal of Steroid Biochemistry and Molecular Biology. 2020 Oct 1;203:105751.

126. Torjesen I. Evidence does not support vitamin D for reducing respiratory infections, reviews conclude. BMJ. 2020 Jun 30;369:m2629.

127. Advies 9620 - Vitamine D, zink en COVID-19 [Internet]. FOD Volksgezondheid. 2021 [cited 2021 Feb 5]. Available from: https://www.health.belgium.be/nl/advies-9620-vitamine-d-zink-en-covid-19

128. Mitjà O, Corbacho-Monné M, Ubals M, Alemany A, Suñer C, Tebé C, et al. A Cluster-Randomized Trial of Hydroxychloroquine for Prevention of Covid-19. New England Journal of Medicine. 2020 Nov 24;0(0):null.

129. Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC, et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. New England Journal of Medicine. 2020 Aug 6;383(6):517–25.

130. Krammer F. SARS-CoV-2 vaccines in development. Nature. 2020 Oct;586(7830):516–27.

131. Le TT, Andreadakis Z, Kumar A, Román RG, Tollefsen S, Saville M, et al. The COVID-19 vaccine development landscape. Nature Reviews Drug Discovery [Internet]. 2020 Apr 9 [cited 2020 Apr 13]; Available from: https://www.nature.com/articles/d41573-020-00073-5

132. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. New England Journal of Medicine. 2021 Feb 4;384(5):403–16.

133. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. New England Journal of Medicine [Internet]. 2020 Dec 10 [cited 2021 Feb 8]; Available from: https://www.nejm.org/doi/10.1056/NEJMoa2034577

134. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK - The Lancet [Internet]. [cited 2021 Feb 8]. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32661-1/fulltext

135. Logunov DY, Dolzhikova IV, Zubkova OV, Tukhvatullin AI, Shcheblyakov DV, Dzharullaeva AS, et al. Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia. Lancet. 2020 26;396(10255):887–97.

136. COVID-19 vaccine surveillance report - week 36. :33.

137. Bernal JL, Andrews N, Gower C, Robertson C, Stowe J, Tessier E, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. BMJ. 2021 May 13;373:n1088.

138. Hall VJ, Foulkes S, Saei A, Andrews N, Oguti B, Charlett A, et al. COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multicentre, cohort study. The Lancet [Internet]. 2021 Apr 23 [cited 2021 Apr 29];0(0). Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00790-X/abstract

139. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. New England Journal of Medicine [Internet]. 2021 Feb 24 [cited 2021 Mar 1]; Available from: https://www.nejm.org/doi/10.1056/NEJMoa2101765

140. Amit S, Regev-Yochay G, Afek A, Kreiss Y, Leshem E. Early rate reductions of SARS-CoV-2 infection and COVID-19 in BNT162b2 vaccine recipients. The Lancet. 2021 Mar 6;397(10277):875–7.

141. Thompson MG. Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers — Eight U.S. Locations, December 2020–March 2021. MMWR Morb Mortal Wkly Rep [Internet]. 2021 [cited 2021 Mar 30];70. Available from: https://www.cdc.gov/mmwr/volumes/70/wr/mm7013e3.htm

142. Moustsen-Helms IR, Emborg H-D, Nielsen J, Nielsen KF, Krause TG, Molbak K, et al. Vaccine effectiveness after 1st and 2nd dose of the BNT162b2 mRNA Covid-19 Vaccine in long-term care facility residents and healthcare workers – a Danish cohort study. medRxiv. 2021 Mar 9;2021.03.08.21252200.

143. Yelin I, Katz R, Herzel E, Berman-Zilberstein T, Ben-Tov A, Kuint J, et al. Associations of the BNT162b2 COVID-19 vaccine effectiveness with patient age and comorbidities. medRxiv. 2021 Mar 17;2021.03.16.21253686.

144. Shah ASV, Gribben C, Bishop J, Hanlon P, Caldwell D, Wood R, et al. Effect of vaccination on transmission of COVID-19: an observational study in healthcare workers and their households. medRxiv. 2021 Mar 21;2021.03.11.21253275.

145. Fabiani M, Ramigni M, Gobbetto V, Mateo-Urdiales A, Pezzotti P, Piovesan C. Effectiveness of the Comirnaty (BNT162b2, BioNTech/Pfizer) vaccine in preventing SARS-CoV-2 infection among healthcare workers, Treviso province, Veneto region, Italy, 27 December 2020 to 24 March 2021. Eurosurveillance [Internet]. 2021 Apr 29 [cited 2021 May 3];26(17). Available from: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2021.26.17.2100420

146. Haas EJ, Angulo FJ, McLaughlin JM, Anis E, Singer SR, Khan F, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. The Lancet [Internet]. 2021 May 5 [cited 2021 May 6];0(0). Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00947-8/abstract

147. Lumley SF, Rodger G, Constantinides B, Sanderson N, Chau KK, Street TL, et al. An observational cohort study on the incidence of SARS-CoV-2 infection and B.1.1.7 variant infection in healthcare workers by antibody and vaccination status. medRxiv. 2021 Mar 12;2021.03.09.21253218.

148. Pritchard E, Matthews P, Stoesser N, Eyre D, Gethings O, Vitha K-D, et al. Impact of vaccination on SARS-CoV-2 cases in the community: a population-based study using the UK COVID-19 Infection Survey. medRxiv. 2021 Apr 23;2021.04.22.21255913.

149. Bjork J, Inghammar M, Moghaddassi M, Rasmussen M, Malmqvist U, Kahn F. Effectiveness of the BNT162b2 vaccine in preventing COVID-19 in the working age population - first results from a cohort study in Southern Sweden. medRxiv. 2021 Apr 21;2021.04.20.21254636.

150. Andrejko K, Pry J, Myers JF, Jewell NP, Openshaw J, Watt J, et al. Early evidence of COVID-19 vaccine effectiveness within the general population of California. medRxiv. 2021 Apr 10;2021.04.08.21255135.

151. Tang L, Hijano DR, Gaur AH, Geiger TL, Neufeld EJ, Hoffman JM, et al. Asymptomatic and Symptomatic SARS-CoV-2 Infections After BNT162b2 Vaccination in a Routinely Screened Workforce. JAMA [Internet]. 2021 May 6 [cited 2021 May 10]; Available from: https://jamanetwork.com/journals/jama/fullarticle/2779854

152. Angel Y, Spitzer A, Henig O, Saiag E, Sprecher E, Padova H, et al. Association Between Vaccination With BNT162b2 and Incidence of Symptomatic and Asymptomatic SARS-CoV-2 Infections Among Health Care Workers. JAMA [Internet]. 2021 May 6 [cited 2021 May 10]; Available from: https://jamanetwork.com/journals/jama/fullarticle/2779853

153. Martínez-Baz I, Miqueleiz A, Casado I, Navascués A, Trobajo-Sanmartín C, Burgui C, et al. Effectiveness of COVID-19 vaccines in preventing SARS-CoV-2 infection and hospitalisation, Navarre, Spain, January to April 2021. Eurosurveillance. 2021 May 27;26(21):2100438.

154. Flacco ME, Soldato G, Acuti Martellucci C, Carota R, Di Luzio R, Caponetti A, et al. Interim Estimates of COVID-19 Vaccine Effectiveness in a Mass Vaccination Setting: Data from an Italian Province. Vaccines (Basel). 2021 Jun 10;9(6):628.

155. Thompson MG, Burgess JL, Naleway AL, Tyner H, Yoon SK, Meece J, et al. Prevention and Attenuation of Covid-19 with the BNT162b2 and mRNA-1273 Vaccines. New England Journal of Medicine [Internet]. 2021 Jun 30 [cited 2021 Jul 6]; Available from: https://www.nejm.org/doi/10.1056/NEJMoa2107058

156. Zacay G, Shasha D, Bareket R, Kadim I, Hershkowitz Sikron F, Tsamir J, et al. BNT162b2 Vaccine Effectiveness in Preventing Asymptomatic Infection With SARS-CoV-2 Virus: A Nationwide Historical Cohort Study. Open Forum Infect Dis. 2021 Jun 9;8(6):ofab262.

157. Mazagatos C, Monge S, Olmedo C, Vega L, Gallego P, Martín-Merino E, et al. Effectiveness of mRNA COVID-19 vaccines in preventing SARS-CoV-2 infections and COVID-19 hospitalisations and deaths in elderly long-term care facility residents, Spain, weeks 53 2020 to 13 2021. Euro Surveill. 2021 Jun;26(24).

158. Azamgarhi T, Hodgkinson M, Shah A, Skinner JA, Hauptmannova I, Briggs TWR, et al. BNT162b2 vaccine uptake and effectiveness in UK healthcare workers - a single centre cohort study. Nat Commun. 2021 Jun 17;12(1):3698.

159. Nasreen S, He S, Chung H, Brown KA, Gubbay JB, Buchan SA, et al. Effectiveness of COVID-19 vaccines against variants of concern, Canada. medRxiv. 2021 Jul 3;2021.06.28.21259420.

160. Vasileiou E, Simpson CR, Shi T, Kerr S, Agrawal U, Akbari A, et al. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. The Lancet [Internet]. 2021 Apr 23 [cited 2021 Apr 29];0(0). Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00677-2/abstract

161. Hyams C, Marlow R, Maseko Z, King J, Ward L, Fox K, et al. Effectiveness of BNT162b2 and ChAdOx1 nCoV-19 COVID-19 vaccination at preventing hospitalisations in people aged at least 80 years: a test-negative, case-control study. Lancet Infect Dis. 2021 Jun 23;S1473-3099(21)00330-3.

162. Vahidy FS, Pischel L, Tano ME, Pan AP, Boom ML, Sostman HD, et al. Real World Effectiveness of COVID-19 mRNA Vaccines against Hospitalizations and Deaths in the United States. medRxiv. 2021 Apr 23;2021.04.21.21255873.

163. Mason TFD, Whitston M, Hodgson J, Watkinson RE, Lau Y-S, Abdulrazeg O, et al. Effects of BNT162b2 mRNA vaccine on Covid-19 infection and hospitalisation among older people: matched case control study for England. medRxiv. 2021 Apr 22;2021.04.19.21255461.

164. Kissling E, Hooiveld M, Martín VS, Martínez-Baz I, William N, Vilcu A-M, et al. Vaccine effectiveness against symptomatic SARS-CoV-2 infection in adults aged 65 years and older in primary care: I-MOVE-COVID-19 project, Europe, December 2020 to May 2021. Eurosurveillance. 2021 Jul 22;26(29):2100670.

165. Bruxvoort K, Sy LS, Qian L, Ackerson BK, Luo Y, Lee GS, et al. Real-World Effectiveness of the mRNA-1273 Vaccine Against COVID-19: Interim Results from a Prospective Observational Cohort Study. SSRN Journal [Internet]. 2021 [cited 2021 Sep 14]; Available from: https://www.ssrn.com/abstract=3916094

166. Harder T, Koch J, Vygen-Bonnet S, Külper-Schiek W, Pilic A, Reda S, et al. Efficacy and effectiveness of COVID-19 vaccines against SARS-CoV-2 infection: interim results of a living systematic review, 1 January to 14 May 2021. Eurosurveillance. 2021 Jul 15;26(28):2100563.

167. Kow CS, Hasan SS. Real-world effectiveness of BNT162b2 mRNA vaccine: a meta-analysis of large observational studies. Inflammopharmacology. 2021 Aug;29(4):1075–90.

168. Iheanacho CO, Eze UIH, Adida EA. A systematic review of effectiveness of BNT162b2 mRNA and ChAdOx1 adenoviral vector COVID-19 vaccines in the general population. Bull Natl Res Cent. 2021;45(1):150.

169. Bernal JL, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. New England Journal of Medicine [Internet]. 2021 Jul 21 [cited 2021 Sep 20]; Available from: https://www.nejm.org/doi/10.1056/NEJMoa2108891

170. Pouwels KB, Pritchard E, Matthews PC, Stoesser N, Eyre DW, Vihta K-D, et al. Impact of Delta on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK [Internet]. 2021 Aug [cited 2021 Sep 9] p. 2021.08.18.21262237. Available from: https://www.medrxiv.org/content/10.1101/2021.08.18.21262237v1

171. Puranik A, Lenehan PJ, Silvert E, Niesen MJM, Corchado-Garcia J, O'Horo JC, et al. Comparison of two highly-effective mRNA vaccines for COVID-19 during periods of Alpha and Delta variant prevalence [Internet]. 2021 Aug [cited 2021 Aug 25] p. 2021.08.06.21261707. Available from: https://www.medrxiv.org/content/10.1101/2021.08.06.21261707v3

172. Bajema KL. Effectiveness of COVID-19 mRNA Vaccines Against COVID-19–Associated Hospitalization — Five Veterans Affairs Medical Centers, United States, February 1–August 6, 2021. MMWR Morb Mortal Wkly Rep [Internet]. 2021 [cited 2021 Sep 20];70. Available from: https://www.cdc.gov/mmwr/volumes/70/wr/mm7037e3.htm

173. Grannis SJ. Interim Estimates of COVID-19 Vaccine Effectiveness Against COVID-19–Associated Emergency Department or Urgent Care Clinic Encounters and Hospitalizations Among Adults During SARS-CoV-2 B.1.617.2 (Delta) Variant Predominance — Nine States, June–August 2021. MMWR Morb Mortal Wkly Rep [Internet]. 2021 [cited 2021 Sep 20];70. Available from: https://www.cdc.gov/mmwr/volumes/70/wr/mm7037e2.htm

174. Corchado-Garcia J, Puyraimond-Zemmour D, Hughes T, Cristea-Platon T, Lenehan P, Pawlowski C, et al. Real-world effectiveness of Ad26.COV2.S adenoviral vector vaccine for COVID-19. medRxiv. 2021 Apr 30;2021.04.27.21256193.

175. Braeye T, Cornelissen L, Catteau L, Haarhuis F, Proesmans K, De Ridder K, et al. Vaccine effectiveness against infection and onwards transmission of COVID-19: Analysis of Belgian contact tracing data, January-June 2021. Vaccine. 2021 Aug 19;S0264-410X(21)01108-7.

176. Zhou D, Dejnirattisai W, Supasa P, Liu C, Mentzer AJ, Ginn HM, et al. Evidence of escape of SARS-CoV-2 variant B.1.351 from natural and vaccine-induced sera. Cell [Internet]. 2021 Feb 23 [cited 2021 Mar 30]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7901269/

177. Kuzmina A, Khalaila Y, Voloshin O, Keren-Naus A, Bohehm L, Raviv Y, et al. SARS CoV-2 spike variants exhibit differential infectivity and neutralization resistance to convalescent or post-vaccination sera. Cell Host & Microbe [Internet]. 2021 Mar 20 [cited 2021 Mar 30]; Available from: https://www.sciencedirect.com/science/article/pii/S1931312821001360

178. Wang Z, Schmidt F, Weisblum Y, Muecksch F, Barnes CO, Finkin S, et al. mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants. Nature. 2021 Feb 10;

179. Dejnirattisai W, Zhou D, Supasa P, Liu C, Mentzer AJ, Ginn HM, et al. Antibody evasion by the Brazilian P.1 strain of SARS-CoV-2. bioRxiv. 2021 Mar 19;2021.03.12.435194.

180. Wu K, Werner AP, Koch M, Choi A, Narayanan E, Stewart-Jones GBE, et al. Serum Neutralizing Activity Elicited by mRNA-1273 Vaccine. New England Journal of Medicine. 2021 Feb 17;0(0):null.

181. Shen X, Tang H, Pajon R, Smith G, Glenn GM, Shi W, et al. Neutralization of SARS-CoV-2 Variants B.1.429 and B.1.351. n engl j med. 2021;3.

182. Edara VV, Norwood C, Floyd K, Lai L, Davis-Gardner ME, Hudson WH, et al. Infection- and vaccine-induced antibody binding and neutralization of the B.1.351 SARS-CoV-2 variant. Cell Host & Microbe. 2021 Apr;29(4):516-521.e3.

183. Zhou D, Dejnirattisai W, Supasa P, Liu C, Mentzer AJ, Ginn HM, et al. Evidence of escape of SARS-CoV-2 variant B.1.351 from natural and vaccine induced sera. Cell [Internet]. 2021 Feb 23 [cited 2021 Mar 8]; Available from: https://www.sciencedirect.com/science/article/pii/S0092867421002269

184. Jongeneelen M, Kaszas K, Veldman D, Huizingh J, Vlugt R van der, Schouten T, et al. Ad26.COV2.S elicited neutralizing activity against Delta and other SARS-CoV-2 variants of concern. bioRxiv. 2021 Jul 1;2021.07.01.450707.

185. Alter G, Yu J, Liu J, Chandrashekar A, Borducchi EN, Tostanoski LH, et al. Immunogenicity of Ad26.COV2.S vaccine against SARS-CoV-2 variants in humans. Nature. 2021 Jun 9;1–5.

186. Wang P, Casner RG, Nair MS, Wang M, Yu J, Cerutti G, et al. Increased Resistance of SARS-CoV-2 Variant P.1 to Antibody Neutralization. bioRxiv. 2021 Apr 9;2021.03.01.433466.

187. Madhi SA, Baillie V, Cutland CL, Voysey M, Koen AL, Fairlie L, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant. New England Journal of Medicine [Internet]. 2021 Mar 16 [cited 2021 Mar 23]; Available from: https://www.nejm.org/doi/10.1056/NEJMoa2102214

188. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. The Lancet [Internet]. 2020 Dec 8 [cited 2020 Dec 14];0(0). Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32661-1/abstract

189. Pfizer and BioNTech Confirm High Efficacy and No Serious Safety Concerns Through Up to Six Months Following Second Dose in Updated Topline Analysis of Landmark COVID-19 Vaccine Study [Internet]. [cited 2021 Sep 8]. Available from: https://investors.pfizer.com/investor-news/press-release-details/2021/Pfizer-and-BioNTech-Confirm-High-Efficacy-and-No-Serious-Safety-Concerns-Through-Up-to-Six-Months-Following-Second-Dose-in-Updated-Topline-Analysis-of-Landmark-COVID-19-Vaccine-Study/default.aspx

190. Abu-Raddad LJ, Chemaitelly H, Butt AA. Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants. New England Journal of Medicine. 2021 May 5;0(0):null.

191. Abu-Raddad LJ, Chemaitelly H, Yassine HM, Benslimane FM, Al Khatib HA, Tang P, et al. Pfizer-BioNTech mRNA BNT162b2 Covid-19 vaccine protection against variants of concern after one versus two doses. Journal of Travel Medicine [Internet]. 2021 May 28 [cited 2021 Jun 7];(taab083). Available from: https://doi.org/10.1093/jtm/taab083

192. Kustin T, Harel N, Finkel U, Perchik S, Harari S, Tahor M, et al. Evidence for increased breakthrough rates of SARS-CoV-2 variants of concern in BNT162b2 mRNA vaccinated individuals. medRxiv. 2021 Apr 16;2021.04.06.21254882.

193. Planas D, Veyer D, Baidaliuk A, Staropoli I, Guivel-Benhassine F, Rajah MM, et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. Nature. 2021 Jul 8;1–7.

194. Yadav PD, Sapkal GN, Ella R, Sahay RR, Nyayanit DA, Patil DY, et al. Neutralization against B.1.351 and B.1.617.2 with sera of COVID-19 recovered cases and vaccinees of BBV152. bioRxiv. 2021 Jun 7;2021.06.05.447177.

195. Liu C, Ginn HM, Dejnirattisai W, Supasa P, Wang B, Tuekprakhon A, et al. Reduced neutralization of SARS-CoV-2 B.1.617 by vaccine and convalescent serum. Cell [Internet]. 2021 Jun 17 [cited 2021 Jul 8]; Available from: https://www.sciencedirect.com/science/article/pii/S0092867421007558

196. SARS-CoV-2 variants of concern and variants under investigation. :71.

197. Choi A, Koch M, Wu K, Dixon G, Oestreicher J, Legault H, et al. Serum Neutralizing Activity of mRNA-1273 against SARS-CoV-2 Variants [Internet]. Microbiology; 2021 Jun [cited 2021 Jul 1]. Available from: http://biorxiv.org/lookup/doi/10.1101/2021.06.28.449914

198. Tada T, Zhou H, Dcosta BM, Samanovic MI, Mulligan MJ, Landau NR. The Spike Proteins of SARS-CoV-2 B.1.617 and B.1.618 Variants Identified in India Provide Partial Resistance to Vaccine-elicited and Therapeutic Monoclonal Antibodies. bioRxiv. 2021 May 16;2021.05.14.444076.

199. Harder T, Külper-Schiek W, Reda S, Treskova-Schwarzbach M, Koch J, Vygen-Bonnet S, et al. Effectiveness of COVID-19 vaccines against SARS-CoV-2 infection with the Delta (B.1.617.2) variant: second interim results of a living systematic review and meta-analysis, 1 January to 25 August 2021. Eurosurveillance. 2021 Oct 14;26(41):2100920.

200. Elliott P, Haw D, Wang H, Eales O, Walters C, Ainslie K, et al. REACT-1 round 13 final report: exponential growth, high prevalence of SARS-CoV-2 and vaccine effectiveness associated with Delta variant in England during May to July 2021 [Internet]. 2021 Aug [cited 2021 Aug 8]. Available from: http://spiral.imperial.ac.uk/handle/10044/1/90800

201. Fowlkes A. Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers Before and During B.1.617.2 (Delta) Variant Predominance — Eight U.S. Locations, December 2020–August 2021. MMWR Morb Mortal Wkly Rep [Internet]. 2021 [cited 2021 Sep 9];70. Available from: https://www.cdc.gov/mmwr/volumes/70/wr/mm7034e4.htm

202. Nanduri S. Effectiveness of Pfizer-BioNTech and Moderna Vaccines in Preventing SARS-CoV-2 Infection Among Nursing Home Residents Before and During Widespread Circulation of the SARS-CoV-2 B.1.617.2 (Delta) Variant — National Healthcare Safety Network, March 1–August 1, 2021. MMWR Morb Mortal Wkly Rep [Internet]. 2021 [cited 2021 Aug 19];70. Available from: https://www.cdc.gov/mmwr/volumes/70/wr/mm7034e3.htm

203. Pramod S, Govindan D, Ramasubramani P, Kar SS, Aggarwal R, Group J vaccine effectiveness study, et al. Effectiveness of Covishield vaccine in preventing Covid-19 – A test-negative case-control study [Internet]. 2021 Jul [cited 2021 Oct 18] p. 2021.07.19.21260693. Available from: https://www.medrxiv.org/content/10.1101/2021.07.19.21260693v1

204. Rosenberg ES. New COVID-19 Cases and Hospitalizations Among Adults, by Vaccination Status — New York, May 3–July 25, 2021. MMWR Morb Mortal Wkly Rep [Internet]. 2021 [cited 2021 Aug 19];70. Available from: https://www.cdc.gov/mmwr/volumes/70/wr/mm7034e1.htm

205. Sheikh A, McMenamin J, Taylor B, Robertson C. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. The Lancet [Internet]. 2021 Jun 14 [cited 2021 Jun 17];0(0). Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01358-1/abstract

206. Tang P, Hasan MR, Chemaitelly H, Yassine HM, Benslimane FM, Khatib HAA, et al. BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the Delta (B.1.617.2) variant in Qatar [Internet]. 2021 Aug [cited 2021 Sep 22] p. 2021.08.11.21261885. Available from: https://www.medrxiv.org/content/10.1101/2021.08.11.21261885v1

207. Tartof SY, Slezak JM, Fischer H, Hong V, Ackerson BK, Ranasinghe ON, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. The Lancet. 2021 Oct 16;398(10309):1407–16.

208. Herlihy R. Rapid Increase in Circulation of the SARS-CoV-2 B.1.617.2 (Delta) Variant — Mesa County, Colorado, April–June 2021. MMWR Morb Mortal Wkly Rep [Internet]. 2021 [cited 2021 Oct 18];70. Available from: https://www.cdc.gov/mmwr/volumes/70/wr/mm7032e2.htm

209. Keegan LT, Truelove S, Lessler J. Progress of the Delta variant and erosion of vaccine effectiveness, a warning from Utah [Internet]. 2021 Aug [cited 2021 Oct 18] p. 2021.08.09.21261554. Available from: https://www.medrxiv.org/content/10.1101/2021.08.09.21261554v1

210. Thiruvengadam R, Awasthi A, Medigeshi G, Bhattacharya S, Mani S, Sivasubbu S, et al. Cellular Immune Responses are Preserved and May Contribute to Chadox1 ChAdOx1 nCoV-19 Vaccine Effectiveness Against Infection Due to SARS-CoV-2 B·1·617·2 Delta Variant Despite Reduced Virus Neutralisation [Internet]. Rochester, NY: Social Science Research Network; 2021 Jul [cited 2021 Oct 18]. Report No.: ID 3884946. Available from: https://papers.ssrn.com/abstract=3884946

211. Chia PY, Xiang Ong SW, Chiew CJ, Ang LW, Chavatte J-M, Mak T-M, et al. Virological and serological kinetics of SARS-CoV-2 Delta variant vaccine-breakthrough infections: a multi-center cohort study [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Jul [cited 2021 Sep 3]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.07.28.21261295

212. LopezBernal J. Effectiveness of COVID-19 vaccines against hospital admission with the Delta (B.1.617.2) variant. :3.

213. Public library - PHE national - Knowledge Hub [Internet]. [cited 2021 Jun 17]. Available from: https://khub.net/web/phe-national/public-library/-/document_library/v2WsRK3ZlEig/view_file/479607329?_com_liferay_document_library_web_portlet_DLPortlet_INSTANCE_v2WsRK3ZlEig_redirect=https%3A%2F%2Fkhub.net%3A443%2Fweb%2Fphe-national%2Fpublic-library%2F-%2Fdocument_library%2Fv2WsRK3ZlEig%2Fview%2F479607266

214. Keehner J, Horton LE, Binkin NJ, Laurent LC, Pride D, Longhurst CA, et al. Resurgence of SARS-CoV-2 Infection in a Highly Vaccinated Health System Workforce. N Engl J Med. 2021 Sep 1;

215. Musser JM, Christensen PA, Olsen RJ, Long SW, Subedi S, Davis JJ, et al. Delta variants of SARS-CoV-2 cause significantly increased vaccine breakthrough COVID-19 cases in Houston, Texas. medRxiv. 2021 Aug 1;2021.07.19.21260808.

216. Cohn BA, Cirillo PM, Murphy CC, Krigbaum NY, Wallace AW. SARS-CoV-2 vaccine protection and deaths among US veterans during 2021. Science. 0(0):eabm0620.

217. Ranzani OT, Hitchings M, Dorion M, D'Agostini TL, Paula RC de, Paula OFP de, et al. Effectiveness of the CoronaVac vaccine in the elderly population during a P.1 variant-associated epidemic of COVID-19 in Brazil: A test-negative case-control study [Internet]. 2021 May [cited 2021

Sep 14] p. 2021.05.19.21257472. Available from: https://www.medrxiv.org/content/10.1101/2021.05.19.21257472v2

218. Shrotri M, Krutikov M, Palmer T, Giddings R, Azmi B, Subbarao S, et al. Vaccine effectiveness of the first dose of ChAdOx1 nCoV-19 and BNT162b2 against SARS-CoV-2 infection in residents of Long-Term Care Facilities (VIVALDI study). medRxiv. 2021 Mar 26;2021.03.26.21254391.

219. Pannus P, Neven KY, Craeye SD, Heyndrickx L, Kerckhove SV, Georges D, et al. Poor antibody response to BioNTech/Pfizer COVID-19 vaccination in SARS-CoV-2 naïve residents of nursing homes. medRxiv. 2021 Jun 9;2021.06.08.21258366.

220. SARS-CoV-2 seroprevalence among nursing home residents and staff in Belgium - Results visit 2 – April 2021 [Internet]. Available from: https://www.sciensano.be/fr/biblio/sars-cov-2-seroprevalence-among-nursing-home-residents-and-staff-belgium-results-visit-2-april-2021

221. Boyarsky BJ, Werbel WA, Avery RK, Tobian AAR, Massie AB, Segev DL, et al. Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients. JAMA. 2021 Jun 1;325(21):2204–6.

222. Chavarot N, Ouedrani A, Marion O, Leruez-Ville M, Vilain E, Baaziz M, et al. Poor Anti-SARS-CoV-2 Humoral and T-cell Responses After 2 Injections of mRNA Vaccine in Kidney Transplant Recipients Treated With Belatacept. Transplantation. 2021 Sep 1;105(9):e94–5.

223. Grupper A, Katchman H. Reduced humoral response to mRNA SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients without prior exposure to the virus: Not alarming, but should be taken gravely. Am J Transplant. 2021 Aug;21(8):2909.

224. Itzhaki Ben Zadok O, Shaul AA, Ben-Avraham B, Yaari V, Ben Zvi H, Shostak Y, et al. Immunogenicity of the BNT162b2 mRNA vaccine in heart transplant recipients - a prospective cohort study. Eur J Heart Fail. 2021 Sep;23(9):1555–9.

225. Rabinowich L, Grupper A, Baruch R, Ben-Yehoyada M, Halperin T, Turner D, et al. Low immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients. J Hepatol. 2021 Aug;75(2):435–8.

226. Rozen-Zvi B, Yahav D, Agur T, Zingerman B, Ben-Zvi H, Atamna A, et al. Antibody response to SARS-CoV-2 mRNA vaccine among kidney transplant recipients: a prospective cohort study. Clin Microbiol Infect. 2021 Aug;27(8):1173.e1-1173.e4.

227. Herishanu Y, Avivi I, Aharon A, Shefer G, Levi S, Bronstein Y, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. Blood. 2021 Jun 10;137(23):3165–73.

228. Monin L, Laing AG, Muñoz-Ruiz M, McKenzie DR, Del Molino Del Barrio I, Alaguthurai T, et al. Safety and immunogenicity of one versus two doses of the COVID-19 vaccine BNT162b2 for patients with cancer: interim analysis of a prospective observational study. Lancet Oncol. 2021 Jun;22(6):765–78.

229. Simon B, Rubey H, Treipl A, Gromann M, Hemedi B, Zehetmayer S, et al. Haemodialysis patients show a highly diminished antibody response after COVID-19 mRNA vaccination compared with healthy controls. Nephrol Dial Transplant. 2021 Aug 27;36(9):1709–16.

230. Broseta JJ, Rodríguez-Espinosa D, Rodríguez N, Mosquera MDM, Marcos MÁ, Egri N, et al. Humoral and Cellular Responses to mRNA-1273 and BNT162b2 SARS-CoV-2 Vaccines Administered to Hemodialysis Patients. Am J Kidney Dis. 2021 Jun 24;S0272-6386(21)00689-2.

231. Chodick G, Tene L, Patalon T, Gazit S, Tov AB, Cohen D, et al. The effectiveness of the first dose of BNT162b2 vaccine in reducing SARS-CoV-2 infection 13-24 days after immunization: real-world evidence. medRxiv. 2021 Jan 29;2021.01.27.21250612.

232. Khan N, Mahmud N. Effectiveness of SARS-CoV-2 Vaccination in a Veterans Affairs Cohort of Patients With Inflammatory Bowel Disease With Diverse Exposure to Immunosuppressive Medications. Gastroenterology. 2021 Sep;161(3):827–36.

233. Effectiveness of SARS-CoV-2 mRNA Vaccines for Preventing Covid-19 Hospitalizations in the United States | medRxiv [Internet]. [cited 2021 Sep 22]. Available from: https://www.medrxiv.org/content/10.1101/2021.07.08.21259776v1

234. Brosh-Nissimov T, Orenbuch-Harroch E, Chowers M, Elbaz M, Nesher L, Stein M, et al. BNT162b2 vaccine breakthrough: clinical characteristics of 152 fully vaccinated hospitalized COVID-19 patients in Israel. Clin Microbiol Infect. 2021 Jul 7;S1198-743X(21)00367-0.

235. Harris RJ, Hall JA, Zaidi A, Andrews NJ, Dunbar JK, Dabrera G. Effect of Vaccination on Household Transmission of SARS-CoV-2 in England. N Engl J Med. 2021 Jun 23;

236. Prunas O, Warren JL, Crawford FW, Gazit S, Patalon T, Weinberger DM, et al. Vaccination with BNT162b2 reduces transmission of SARS-CoV-2 to household contacts in Israel. medRxiv. 2021 Jul 16;2021.07.13.21260393.

237. Layan M, Gilboa M, Gonen T, Goldenfeld M, Meltzer L, Andronico A, et al. Impact of BNT162b2 vaccination and isolation on SARS-CoV-2 transmission in Israeli households: an observational study. medRxiv. 2021 Jul 16;2021.07.12.21260377.

238. Gier B de, Andeweg S, Joosten R, Schegget R ter, Smorenburg N, Kassteele J van de, et al. Vaccine effectiveness against SARS-CoV-2 transmission and infections among household and other close contacts of confirmed cases, the Netherlands, February to May 2021. Eurosurveillance. 2021 Aug 5;26(31):2100640.

239. Increased Household Transmission of COVID-19 Cases Associated with SARS-CoV-2 Variant of Concern B.1.617.2: A national case-control study. :21.

240. Singanayagam A, Hakki S, Dunning J, Madon KJ, Crone MA, Koycheva A, et al. Community transmission and viral load kinetics of the SARS-CoV-2 delta (B.1.617.2) variant in vaccinated and unvaccinated individuals in the UK: a prospective, longitudinal, cohort study. Lancet Infect Dis. 2021 Oct 29;S1473-3099(21)00648-4.

241. Borobia AM, Carcas AJ, Pérez-Olmeda M, Castaño L, Bertran MJ, García-Pérez J, et al. Immunogenicity and reactogenicity of BNT162b2 booster in ChAdOx1-S-primed participants (CombiVacS): a multicentre, open-label, randomised, controlled, phase 2 trial. Lancet. 2021 Jun 25;S0140-6736(21)01420-3.

242. Hillus D, Schwarz T, Tober-Lau P, Hastor H, Thibeault C, Kasper S, et al. Safety, reactogenicity, and immunogenicity of homologous and heterologous prime-boost immunisation with ChAdOx1-nCoV19 and BNT162b2: a prospective cohort study. medRxiv. 2021 Jun 2;2021.05.19.21257334.

243. Shaw RH, Stuart A, Greenland M, Liu X, Van-Tam JSN, Snape MD. Heterologous prime-boost COVID-19 vaccination: initial reactogenicity data. The Lancet [Internet]. 2021 May 12 [cited 2021 May 19];0(0). Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01115-6/abstract

244. Groß R, Zanoni M, Seidel A, Conzelmann C, Gilg A, Krnavek D, et al. Heterologous ChAdOx1 nCoV-19 and BNT162b2 prime-boost vaccination elicits potent neutralizing antibody responses and T cell reactivity. medRxiv. 2021 Jun 1;2021.05.30.21257971.

245. Powell AA, Power L, Westrop S, McOwat K, Campbell H, Simmons R, et al. Real-world data shows increased reactogenicity in adults after heterologous compared to homologous prime-boost COVID-19 vaccination, March−June 2021, England. Eurosurveillance. 2021 Jul 15;26(28):2100634.

246. Barros-Martins J, Hammerschmidt SI, Cossmann A, Odak I, Stankov MV, Ramos GM, et al. Humoral and cellular immune response against SARS-CoV-2 variants following heterologous and homologous ChAdOx1 nCoV-19/BNT162b2 vaccination. medRxiv. 2021 Jun 3;2021.06.01.21258172.

247. Vallée A, Vasse M, Mazaux L, Bonan B, Amiel C, Zia-Chahabi S, et al. An Immunogenicity Report for the Comparison between Heterologous and Homologous Prime-Boost Schedules with ChAdOx1-S and BNT162b2 Vaccines. J Clin Med. 2021 Aug 25;10(17):3817.

248. Hammerschmidt SI, Bosnjak B, Bernhardt G, Friedrichsen M, Ravens I, Dopfer-Jablonka A, et al. Neutralization of the SARS-CoV-2 Delta variant after heterologous and homologous BNT162b2 or ChAdOx1 nCoV-19 vaccination. Cell Mol Immunol. 2021 Aug 23;1–2.

249. Normark J, Vikström L, Gwon Y-D, Persson I-L, Edin A, Björsell T, et al. Heterologous ChAdOx1 nCoV-19 and mRNA-1273 Vaccination. New England Journal of Medicine [Internet]. 2021 Jul 14 [cited 2021 Sep 17]; Available from: https://www.nejm.org/doi/10.1056/NEJMc2110716

250. Schmidt T, Klemis V, Schub D, Mihm J, Hielscher F, Marx S, et al. Immunogenicity and reactogenicity of heterologous ChAdOx1 nCoV-19/mRNA vaccination. Nat Med. 2021 Sep;27(9):1530–5.

251. Benning L, Töllner M, Hidmark A, Schaier M, Nusshag C, Kälble F, et al. Heterologous ChAdOx1 nCoV-19/BNT162b2 Prime-Boost Vaccination Induces Strong Humoral Responses among Health Care Workers. Vaccines (Basel). 2021 Aug 4;9(8):857.

252. Gram MA, Nielsen J, Schelde AB, Nielsen KF, Moustsen-Helms IR, Sørensen AKB, et al. Vaccine effectiveness when combining the ChAdOx1 vaccine as the first dose with an mRNA COVID-19 vaccine as the second dose [Internet]. 2021 Jul [cited 2021 Sep 22] p. 2021.07.26.21261130. Available from: https://www.medrxiv.org/content/10.1101/2021.07.26.21261130v1

253. Ho T-C, Chen Y-MA, Chan H-P, Chang C-C, Chuang K-P, Lee C-H, et al. The Effects of Heterologous Immunization with Prime-Boost COVID-19 Vaccination against SARS-CoV-2. Vaccines (Basel). 2021 Oct 11;9(10):1163.

254. Atmar RL, Lyke KE, Deming ME, Jackson LA, Branche AR, Sahly HME, et al. Heterologous SARS-CoV-2 Booster Vaccinations – Preliminary Report [Internet]. 2021 Oct [cited 2021 Oct 18] p. 2021.10.10.21264827. Available from: https://www.medrxiv.org/content/10.1101/2021.10.10.21264827v2

255. Goldberg Y, Mandel M, Bar-On YM, Bodenheimer O, Freedman L, Haas EJ, et al. Waning immunity of the BNT162b2 vaccine: A nationwide study from Israel [Internet]. 2021 Aug [cited 2021 Sep 15] p. 2021.08.24.21262423. Available from: https://www.medrxiv.org/content/10.1101/2021.08.24.21262423v1

256. Tartof SY, Slezak JM, Fischer H, Hong V, Ackerson BK, Ranasinghe ON, et al. Six-Month Effectiveness of BNT162B2 mRNA COVID-19 Vaccine in a Large US Integrated Health System: A Retrospective Cohort Study [Internet]. Rochester, NY: Social Science Research Network; 2021 Aug [cited 2021 Sep 15]. Report No.: ID 3909743. Available from: https://papers.ssrn.com/abstract=3909743

257. Chemaitelly H, Tang P, Hasan MR, AlMukdad S, Yassine HM, Benslimane FM, et al. Waning of BNT162b2 Vaccine Protection against SARS-CoV-2 Infection in Qatar. N Engl J Med. 2021 Oct 6;

258. Andrews N, Tessier E, Stowe J, Gower C, Kirsebom F, Simmons R, et al. Vaccine effectiveness and duration of protection of Comirnaty, Vaxzevria and Spikevax against mild and severe COVID-19 in the UK [Internet]. Epidemiology; 2021 Sep [cited 2021 Oct 25]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.09.15.21263583

259. Nordström P, Ballin M, Nordström A. Effectiveness of Covid-19 Vaccination Against Risk of Symptomatic Infection, Hospitalization, and Death Up to 9 Months: A Swedish Total-Population Cohort Study [Internet]. Rochester, NY: Social Science Research Network; 2021 Oct [cited 2021 Nov 17]. Report No.: ID 3949410. Available from: https://papers.ssrn.com/abstract=3949410

260. Canaday DH, Carias L, Oyebanji OA, Keresztesy D, Wilk D, Payne M, et al. Reduced BNT162b2 mRNA vaccine response in SARS-CoV-2-naive nursing home residents. medRxiv. 2021 Mar 22;2021.03.19.21253920.

261. Pegu A, O'Connell SE, Schmidt SD, O'Dell S, Talana CA, Lai L, et al. Durability of mRNA-1273 vaccine-induced antibodies against SARS-CoV-2 variants. Science. 2021 Sep 17;373(6561):1372–7.

262. Aldridge RW, Yavlinsky A, Nguyen V, Eyre MT, Shrotri M, Navaratnam AMD, et al. Waning of SARS-CoV-2 antibodies targeting the Spike protein in individuals post second dose of ChAdOx1 and BNT162b2 COVID-19 vaccines and risk of breakthrough infections: analysis of the Virus Watch community cohort [Internet]. 2021 Nov [cited 2021 Nov 17] p. 2021.11.05.21265968. Available from: https://www.medrxiv.org/content/10.1101/2021.11.05.21265968v1

263. Charmetant X, Espi M, Benotmane I, Heibel F, Buron F, Gautier-Vargas G, et al. Comparison of infected and vaccinated transplant recipients highlights the role of Tfh and neutralizing IgG in COVID-19 protection [Internet]. 2021 Jul [cited 2021 Sep 22] p. 2021.07.22.21260852. Available from: https://www.medrxiv.org/content/10.1101/2021.07.22.21260852v1

264. Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Del Bello A. Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients. N Engl J Med. 2021 Aug 12;385(7):661–2.

265. Schrezenmeier E, Rincon-Arevalo H, Stefanski A-L, Potekhin A, Staub-Hohenbleicher H, Choi M, et al. B and T cell responses after a third dose of SARS-CoV-2 vaccine in Kidney Transplant Recipients [Internet]. 2021 Aug [cited 2021 Sep 22] p. 2021.08.12.21261966. Available from: https://www.medrxiv.org/content/10.1101/2021.08.12.21261966v2

266. Werbel WA, Boyarsky BJ, Ou MT, Massie AB, Tobian AAR, Garonzik-Wang JM, et al. Safety and Immunogenicity of a Third Dose of SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients: A Case Series. Ann Intern Med. 2021 Sep;174(9):1330–2.

267. Justification, safety, and efficacy of a third dose of mRNA vaccine in maintenance hemodialysis patients: a prospective observational study | medRxiv[Internet]. [cited 2021 Sep 22]. Available from: https://www.medrxiv.org/content/10.1101/2021.07.02.21259913v1

268. Ducloux D, Colladant M, Chabannes M, Yannaraki M, Courivaud C. Humoral response after 3 doses of the BNT162b2 mRNA COVID-19 vaccine in patients on hemodialysis. Kidney Int. 2021 Sep;100(3):702–4.

269. Longlune N, Nogier MB, Miedougé M, Gabilan C, Cartou C, Seigneuric B, et al. High immunogenicity of a messenger RNA-based vaccine against SARS-CoV-2 in chronic dialysis patients. Nephrol Dial Transplant. 2021 Aug 27;36(9):1704–9.

270. Hall VG, Ferreira VH, Ku T, Ierullo M, Majchrzak-Kita B, Chaparro C, et al. Randomized Trial of a Third Dose of mRNA-1273 Vaccine in Transplant Recipients. N Engl J Med. 2021 Aug 11;

271. Falsey AR, Frenck RW, Walsh EE, Kitchin N, Absalon J, Gurtman A, et al. SARS-CoV-2 Neutralization with BNT162b2 Vaccine Dose 3. New England Journal of Medicine. 2021 Oct 21;385(17):1627–9.

272. Pan H, Wu Q, Zeng G, Yang J, Jiang D, Deng X, et al. Immunogenicity and safety of a third dose, and immune persistence of CoronaVac vaccine in healthy adults aged 18-59 years: interim results from a double-blind, randomized, placebo-controlled phase 2 clinical trial [Internet]. 2021 Jul [cited 2021 Sep 22] p. 2021.07.23.21261026. Available from: https://www.medrxiv.org/content/10.1101/2021.07.23.21261026v1

273. Yorsaeng R, Suntronwong N, Phowatthanasathian H, Assawakosri S, Kanokudom S, Thongmee T, et al. Immunogenicity of a third dose viral-vectored COVID-19 vaccine after receiving two-dose inactivated vaccines in healthy adults [Internet]. 2021 Sep [cited 2021 Oct 28] p. 2021.09.16.21263692. Available from: https://www.medrxiv.org/content/10.1101/2021.09.16.21263692v1

274. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Kalkstein N, et al. Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. N Engl J Med. 2021 Oct 7;385(15):1393–400.

275. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Alroy-Preis S, et al. Protection Across Age Groups of BNT162b2 Vaccine Booster against Covid-19 [Internet]. 2021 Oct [cited 2021 Oct 26] p. 2021.10.07.21264626. Available from: https://www.medrxiv.org/content/10.1101/2021.10.07.21264626v1

276. Patalon T, Gazit S, Pitzer VE, Prunas O, Warren JL, Weinberger DM. Short Term Reduction in the Odds of Testing Positive for SARS-CoV-2; a Comparison Between Two Doses and Three doses of the BNT162b2 Vaccine [Internet]. 2021 Aug [cited 2021 Oct 26] p. 2021.08.29.21262792. Available from: https://www.medrxiv.org/content/10.1101/2021.08.29.21262792v1

277. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. New England Journal of Medicine. 2021 Apr 9;0(0):null.

278. Towards Understanding ChAdOx1 nCov-19 Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT) [Internet]. 2021 [cited 2021 May 12]. Available from: https://www.researchsquare.com

279. Gargano JW. Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices — United States, June 2021. MMWR Morb Mortal Wkly Rep [Internet]. 2021 [cited 2021 Jul 12];70. Available from: https://www.cdc.gov/mmwr/volumes/70/wr/mm7027e2.htm

280. Male V. Menstrual changes after covid-19 vaccination. BMJ. 2021 Sep 16;374:n2211.

281. Kharbanda EO, Haapala J, DeSilva M, Vazquez-Benitez G, Vesco KK, Naleway AL, et al. Spontaneous Abortion Following COVID-19 Vaccination During Pregnancy. JAMA [Internet]. 2021 Sep 8 [cited 2021 Sep 21]; Available from: https://doi.org/10.1001/jama.2021.15494

282. Walter EB, Talaat KR, Sabharwal C, Gurtman A, Lockhart S, Paulsen GC, et al. Evaluation of the BNT162b2 Covid-19 Vaccine in Children 5 to 11 Years of Age. New England Journal of Medicine. 2021 Nov 9;0(0):null.

283. Q&A on coronaviruses (COVID-19) [Internet]. [cited 2020 Mar 24]. Available from: https://www.who.int/news-room/q-a-detail/q-a-coronaviruses

284. Bi Q, Wu Y, Mei S, Ye C, Zou X, Zhang Z, et al. Epidemiology and Transmission of COVID-19 in Shenzhen China: Analysis of 391 cases and 1,286 of their close contacts. medRxiv. 2020 Mar 4;2020.03.03.20028423.

285. Burke RM. Active Monitoring of Persons Exposed to Patients with Confirmed COVID-19 — United States, January–February 2020. MMWR Morb Mortal Wkly Rep [Internet]. 2020 [cited 2020 Mar 17];69. Available from: https://www.cdc.gov/mmwr/volumes/69/wr/mm6909e1.htm

286. CDC. Coronavirus Disease 2019 (COVID-19) [Internet]. Centers for Disease Control and Prevention. 2020 [cited 2021 Jul 8]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/surface-transmission.html

287. Mondelli MU, Colaneri M, Seminari EM, Baldanti F, Bruno R. Low risk of SARS-CoV-2 transmission by fomites in real-life conditions. The Lancet Infectious Diseases. 2021 May 1;21(5):e112.

288. Meyerowitz EA, Richterman A, Gandhi RT, Sax PE. Transmission of SARS-CoV-2: A Review of Viral, Host, and Environmental Factors. Ann Intern Med. 2021 Jan;174(1):69–79.

289. Kampf G, Brüggemann Y, Kaba HEJ, Steinmann J, Pfaender S, Scheithauer S, et al. Potential sources, modes of transmission and effectiveness of prevention measures against SARS-CoV-2. J Hosp Infect. 2020 Dec;106(4):678–97.

290. World Health Organization. Transmission of SARS-CoV-2: implications for infection prevention precautions [Internet]. Update 9th July [cited 2020 Jul 14]. Available from: https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions

291. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. JAMA [Internet]. 2020 Mar 11 [cited 2020 Mar 15]; Available from: https://jamanetwork.com/journals/jama/fullarticle/2762997

292. Cai J, Xu J, Lin D, Yang zhi, Xu L, Qu Z, et al. A Case Series of children with 2019 novel coronavirus infection: clinical and epidemiological features. Clinical Infectious Diseases. 2020 Feb 28;ciaa198.

293. Peng L, Liu J, Xu W, Luo Q, Deng K, Lin B, et al. 2019 Novel Coronavirus can be detected in urine, blood, anal swabs and oropharyngeal swabs samples. medRxiv. 2020 Feb 25;2020.02.21.20026179.

294. Wu Y, Guo C, Tang L, Hong Z, Zhou J, Dong X, et al. Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. The Lancet Gastroenterology & Hepatology [Internet]. 2020 Mar 19 [cited 2020 Mar 26];0(0). Available from: https://www.thelancet.com/journals/langas/article/PIIS2468-1253(20)30083-2/abstract

295. Xiao F, Sun J, Xu Y, Li F, Huang X, Li H, et al. Early Release - Infectious SARS-CoV-2 in Feces of Patient with Severe COVID-19 - Volume 26, Number 8—August 2020 - Emerging Infectious Diseases journal - CDC. [cited 2020 Jun 8]; Available from: https://wwwnc.cdc.gov/eid/article/26/8/20-0681_article

296. Zhang Y, Chen C, Zhu S, Shu C, Wang D, Song J, et al. Isolation of 2019-nCoV from a Stool Specimen of a Laboratory-Confirmed Case of the Coronavirus Disease 2019 (COVID-19). CCDCW. 2020 Feb 1;2(8):123–4.

297. Dockery DM, Rowe SG, Murphy MA, Krzystolik MG. The Ocular Manifestations and Transmission of COVID-19; Recommendations for Prevention. The Journal of Emergency Medicine [Internet]. 2020 May 8 [cited 2020 May 11]; Available from: http://www.sciencedirect.com/science/article/pii/S073646792030398X

298. Prematunge C, National Collaborating Centre for Methods and Tools. Emerging Evidence on COVID-19. COVID-19 Summary of Heating, Ventilation, Air Conditioning (HVAC) systems and Transmission of SARS-CoV-2 [Internet]. Emerging Sciense Group; (Emerging Evidence on COVID-19.). Available from: https://www.nccmt.ca/covid-19/covid-19-evidence-reviews/176

299. Zhou J, Otter JA, Price JR, Cimpeanu C, Garcia DM, Kinross J, et al. Investigating SARS-CoV-2 surface and air contamination in an acute healthcare setting during the peak of the COVID-19 pandemic in London. Clin Infect Dis [Internet]. [cited 2020 Sep 5]; Available from: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa905/5868534

300. Santarpia JL, Rivera DN, Herrera VL, Morwitzer MJ, Creager HM, Santarpia GW, et al. Aerosol and surface contamination of SARS-CoV-2 observed in quarantine and isolation care. Scientific Reports. 2020 Jul 29;10(1):12732.

301. Lednicky JA, Lauzardo M, Fan ZH, Jutla A, Tilly TB, Gangwar M, et al. Viable SARS-CoV-2 in the air of a hospital room with COVID-19 patients. Int J Infect Dis. 2020 Nov;100:476–82.

302. Kim Y-I, Kim S-G, Kim S-M, Kim E-H, Park S-J, Yu K-M, et al. Infection and Rapid Transmission of SARS-CoV-2 in Ferrets. Cell Host & Microbe. 2020 May 13;27(5):704-709.e2.

303. Richard M, Kok A, de Meulder D, Bestebroer TM, Lamers MM, Okba NMA, et al. SARS-CoV-2 is transmitted via contact and via the air between ferrets. Nature Communications. 2020 Jul 8;11(1):3496.

304. Xiao S, Li Y, Wong T, Hui DSC. Role of fomites in SARS transmission during the largest hospital outbreak in Hong Kong. PLOS ONE. 2017 Jul 20;12(7):e0181558.

305. Yu IT-S, Qiu H, Tse LA, Wong TW. Severe Acute Respiratory Syndrome Beyond Amoy Gardens: Completing the Incomplete Legacy. Clin Infect Dis. 2014 Mar 1;58(5):683–6.

306. Booth TF, Kournikakis B, Bastien N, Ho J, Kobasa D, Stadnyk L, et al. Detection of Airborne Severe Acute Respiratory Syndrome (SARS) Coronavirus and Environmental Contamination in SARS Outbreak Units. J Infect Dis. 2005 May 1;191(9):1472–7.

307. Park SY, Kim Y-M, Yi S, Lee S, Na B-J, Kim CB, et al. Early Release - Coronavirus Disease Outbreak in Call Center, South Korea - Volume 26, Number 8—August 2020 - Emerging Infectious Diseases journal - CDC. [cited 2020 Jun 25]; Available from: https://wwwnc.cdc.gov/eid/article/26/8/20-1274_article

308. Jang S, Han SH, Rhee J-Y. Cluster of Coronavirus Disease Associated with Fitness Dance Classes, South Korea. Emerging Infect Dis. 2020 Aug;26(8):1917–20.

309. Hamner L. High SARS-CoV-2 Attack Rate Following Exposure at a Choir Practice — Skagit County, Washington, March 2020. MMWR Morb Mortal Wkly Rep [Internet]. 2020 [cited 2020 May 20];69. Available from: https://www.cdc.gov/mmwr/volumes/69/wr/mm6919e6.htm

310. Lu J, Gu J, Li K, Xu C, Su W, Lai Z, et al. COVID-19 Outbreak Associated with Air Conditioning in Restaurant, Guangzhou, China, 2020. Emerging Infect Dis. 2020 Apr 2;26(7).

311. Shen Y, Li C, Dong H, Wang Z, Martinez L, Sun Z, et al. Community Outbreak Investigation of SARS-CoV-2 Transmission Among Bus Riders in Eastern China. JAMA Intern Med [Internet]. 2020 Sep 1 [cited 2020 Sep 3]; Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2770172

312. Alsved M, Matamis A, Bohlin R, Richter M, Bengtsson P-E, Fraenkel C-J, et al. Exhaled respiratory particles during singing and talking. Aerosol Science and Technology. 2020 Aug 24;0(0):1–4.

313. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. Ann Intern Med. 2020 Mar 10;

314. Backer JA, Klinkenberg D, Wallinga J. Incubation period of 2019 novel coronavirus (2019-nCoV) infections among travellers from Wuhan, China, 20–28 January 2020. Eurosurveillance [Internet]. 2020 Feb 6 [cited 2020 Feb 10];25(5). Available from: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.5.2000062

315. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of 2019 novel coronavirus infection in China. New England Journal of Medicine [Internet]. 2020 Feb 28;e-publish. Available from: https://www.nejm.org/doi/10.1056/NEJMoa2002032

316. Yang L, Dai J, Zhao J, Wang Y, Deng P, Wang J. Estimation of incubation period and serial interval of COVID-19: analysis of 178 cases and 131 transmission chains in Hubei province, China. Epidemiology and Infection [Internet]. 2020 [cited 2020 Sep 16];148. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7324649/

317. McAloon CG, Collins A, Hunt K, Barber A, Byrne A, Butler F, et al. The incubation period of COVID-19: A rapid systematic review and meta-analysis of observational research. medRxiv. 2020 Apr 28;2020.04.24.20073957.

318. Wei Y, Wei L, Liu Y, Huang L, Shen S, Zhang R, et al. Comprehensive estimation for the length and dispersion of COVID-19 incubation period: a systematic review and meta-analysis. Infection [Internet]. 2021 Aug 18 [cited 2021 Sep 20]; Available from: https://doi.org/10.1007/s15010-021-01682-x

319. Cereda D, Tirani M, Rovida F, V D, M A, P P, et al. The early phase of the COVID-19 outbreak in Lombardy, Italy. arXiv:200309320 [q-bio] [Internet]. 2020 Mar 20 [cited 2020 Mar 26]; Available from: http://arxiv.org/abs/2003.09320

320. Griffin J, Casey M, Collins Á, Hunt K, McEvoy D, Byrne A, et al. Rapid review of available evidence on the serial interval and generation time of COVID-19. BMJ Open. 2020 Nov 23;10(11):e040263.

321. Rai B, Shukla A, Dwivedi LK. Estimates of serial interval for COVID-19: A systematic review and meta-analysis. Clin Epidemiol Glob Health [Internet]. 2020 Aug 26 [cited 2020 Dec 2]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7448781/

322. Ganyani T, Kremer C, Chen D, Torneri A, Faes C, Wallinga J, et al. Estimating the generation interval for coronavirus disease (COVID-19) based on symptom onset data, March 2020. Euro Surveill. 2020 Apr;25(17).

323. Kang M, Xin H, Yuan J, Ali ST, Liang Z, Zhang J, et al. Transmission dynamics and epidemiological characteristics of Delta variant infections in China. 2021 Aug 13;2021.08.12.21261991.

324. Zhang M, Xiao J, Deng A, Zhang Y, Zhuang Y, Hu T, et al. Transmission Dynamics of an Outbreak of the COVID-19 Delta Variant B.1.617.2 — Guangdong Province, China, May–June 2021. CCDCW. 2021 Jul 2;3(27):584–6.

325. Pung R, Mak TM, Group CC-19 working, Kucharski AJ, Lee VJ. Serial intervals observed in SARS-CoV-2 B.1.617.2 variant cases. 2021 Jun 4;2021.06.04.21258205.

326. Li B, Deng A, Li K, Hu Y, Li Z, Xiong Q, et al. Viral infection and transmission in a large, well-traced outbreak caused by the SARS-CoV-2 Delta variant. 2021 Jul 23;2021.07.07.21260122.

327. Woelfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Mueller MA, et al. Clinical presentation and virological assessment of hospitalized cases of coronavirus disease 2019 in a travel-associated transmission cluster. medRxiv. 2020 Mar 8;2020.03.05.20030502.

328. Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. New England Journal of Medicine. 2020 Feb 19;0(0):null.

329. Xu T, Chen C, Zhu Z, Cui M, Chen C, Dai H, et al. Clinical features and dynamics of viral load in imported and non-imported patients with COVID-19. International Journal of Infectious Diseases. 2020 Mar;S1201971220301417.

330. Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. JAMA [Internet]. 2020 Mar 3 [cited 2020 Mar 26]; Available from: https://jamanetwork.com/journals/jama/fullarticle/2762688

331. To KK-W, Tsang OT-Y, Leung W-S, Tam AR, Wu T-C, Lung DC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. The Lancet Infectious Diseases [Internet]. 2020 Mar 23 [cited 2020 Mar 26]; Available from: http://www.sciencedirect.com/science/article/pii/S1473309920301961

332. Pan Y, Zhang D, Yang P, Poon LLM, Wang Q. Viral load of SARS-CoV-2 in clinical samples. The Lancet Infectious Diseases. 2020 Apr 1;20(4):411–2.

333. He X, Lau EH, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. medRxiv. 2020 Mar 18;2020.03.15.20036707.

334. To KK-W, Tsang OT-Y, Leung W-S, Tam AR, Wu T-C, Lung DC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. The Lancet Infectious Diseases. 2020 May 1;20(5):565–74.

335. Borremans B, Gamble A, Prager KC, Helman SK, McClain AM, Cox C, et al. Quantifying antibody kinetics and RNA detection during early-phase SARS-CoV-2 infection by time since symptom onset. Malagón T, editor. eLife. 2020 Sep 7;9:e60122.

336. Cheng H-Y, Jian S-W, Liu D-P, Ng T-C, Huang W-T, Lin H-H. Contact Tracing Assessment of COVID-19 Transmission Dynamics in Taiwan and Risk at Different Exposure Periods Before and After Symptom Onset. JAMA Intern Med [Internet]. 2020 May 1 [cited 2020 May 11]; Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2765641

337. Luo L, Liu D, Liao X, Wu X, Jing Q, Zheng J, et al. Modes of contact and risk of transmission in COVID-19 among close contacts. medRxiv. 2020 Mar 26;2020.03.24.20042606.

338. Chaw L, Koh WC, Jamaludin SA, Naing L, Alikhan MF, Wong J. SARS-CoV-2 transmission in different settings: Analysis of cases and close contacts from the Tablighi cluster in Brunei Darussalam. medRxiv. 2020 Jul 10;2020.05.04.20090043.

339. Du Z, Wang L, Xu X, Wu Y, Cowling BJ, Meyers LA. The serial interval of COVID-19 from publicly reported confirmed cases. Emerging Infectious Diseases. 2020 Feb 23;20(6):2020.02.19.20025452.

340. Nishiura H, Linton NM, Akhmetzhanov AR. Serial interval of novel coronavirus (COVID-19) infections. Int J Infect Dis. 2020 Mar 4;

341. Qian G, Yang N, Ma AHY, Wang L, Li G, Chen X, et al. A COVID-19 Transmission within a family cluster by presymptomatic infectors in China. Clin Infect Dis. 2020 Mar 23;

342. He X, Lau EHY, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nature Medicine. 2020 Apr 15;1–4.

343. He X, Lau EHY, Wu P, Deng X, Wang J, Hao X, et al. Author Correction: Temporal dynamics in viral shedding and transmissibility of COVID-19. Nature Medicine. 2020 Sep 1;26(9):1491–3.

344. Wei WE. Presymptomatic Transmission of SARS-CoV-2 — Singapore, January 23–March 16, 2020. MMWR Morb Mortal Wkly Rep [Internet]. 2020 [cited 2020 Apr 6];69. Available from: https://www.cdc.gov/mmwr/volumes/69/wr/mm6914e1.htm

345. Buitrago-Garcia D, Egli-Gany D, Counotte MJ, Hossmann S, Imeri H, Ipekci AM, et al. Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: A living systematic review and meta-analysis. PLoS Med. 2020 Sep;17(9):e1003346.

346. Johansson MA, Quandelacy TM, Kada S, Prasad PV, Steele M, Brooks JT, et al. SARS-CoV-2 Transmission From People Without COVID-19 Symptoms. JAMA Netw Open. 2021 Jan 4;4(1):e2035057.

347. Kim M-C, Cui C, Shin K-R, Bae J-Y, Kweon O-J, Lee M-K, et al. Duration of Culturable SARS-CoV-2 in Hospitalized Patients with Covid-19. N Engl J Med. 2021 Jan 27;

348. Folgueira MD, Luczkowiak J, Lasala F, Perez-Rivilla A, Delgado R. Persistent SARS-CoV-2 replication in severe COVID-19. medRxiv. 2020 Jun 12;2020.06.10.20127837.

349. Baang JH, Smith C, Mirabelli C, Valesano AL, Manthei DM, Bachman MA, et al. Prolonged Severe Acute Respiratory Syndrome Coronavirus 2 Replication in an Immunocompromised Patient. J Infect Dis [Internet]. [cited 2020 Dec 1]; Available from: https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiaa666/5934826

350. Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature. 2020;581(7809):465–9.

351. Singanayagam A, Patel M, Charlett A, Lopez Bernal J, Saliba V, Ellis J, et al. Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020. Eurosurveillance [Internet]. 2020 Aug 13 [cited 2020 Aug 17];25(32). Available from: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.32.2001483

352. Levine-Tiefenbrun M, Yelin I, Katz R, Herzel E, Golan Z, Schreiber L, et al. Decreased SARS-CoV-2 viral load following vaccination. medRxiv. 2021 Feb 8;2021.02.06.21251283.

353. Petter E, Mor O, Zuckerman N, Oz-Levi D, Younger A, Aran D, et al. Initial real world evidence for lower viral load of individuals who have been vaccinated by BNT162b2. medRxiv. 2021 Feb 8;2021.02.08.21251329.

354. Kawasuji H, Takegoshi Y, Kaneda M, Ueno A, Miyajima Y, Kawago K, et al. Transmissibility of COVID-19 depends on the viral load around onset in adult and symptomatic patients. PLOS ONE. 2020 Dec 9;15(12):e0243597.

355. Marks M, Millat-Martinez P, Ouchi D, Roberts C h, Alemany A, Corbacho-Monné M, et al. Transmission of COVID-19 in 282 clusters in Catalonia, Spain: a cohort study. The Lancet Infectious Diseases [Internet]. 2021 Feb 2 [cited 2021 Feb 18];0(0). Available from: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30985-3/abstract

356. Prunas O, Warren JL, Crawford FW, Gazit S, Patalon T, Weinberger DM, et al. Vaccination with BNT162b2 reduces transmission of SARS-CoV-2 to household contacts in Israel [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Jul [cited 2021 Sep 8]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.07.13.21260393

357. Gier B de, Andeweg S, Joosten R, Schegget R ter, Smorenburg N, Kassteele J van de, et al. Vaccine effectiveness against SARS-CoV-2 transmission and infections among household and other close contacts of confirmed cases, the Netherlands, February to May 2021. Eurosurveillance. 2021 Aug 5;26(31):2100640.

358. Braeye T, Cornelissen L, Catteau L, Haarhuis F, Proesmans K, De Ridder K, et al. Vaccine effectiveness against infection and onwards transmission of COVID-19: Analysis of Belgian contact tracing data, January-June 2021. Vaccine [Internet]. 2021 Aug 19 [cited 2021 Sep 8]; Available from: https://www.sciencedirect.com/science/article/pii/S0264410X21011087

359. Harris RJ, Hall JA, Zaidi A, Andrews NJ, Dunbar JK, Dabrera G. Effect of Vaccination on Household Transmission of SARS-CoV-2 in England. New England Journal of Medicine. 2021 Aug 19;385(8):759–60.

360. Pouwels KB, Pritchard E, Matthews PC, Stoesser N, Eyre DW, Vihta K-D, et al. Impact of Delta on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK [Internet]. Epidemiology; 2021 Aug [cited 2021 Sep 8]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.08.18.21262237

361. Riemersma KK, Grogan BE, Kita-Yarbro A, Kocharian A, Florek KR, Westergaard R, et al. Shedding of Infectious SARS-CoV-2 Despite Vaccination when the Delta Variant is Prevalent - Wisconsin, July 2021. :9.

362. Brown CM. Outbreak of SARS-CoV-2 Infections, Including COVID-19 Vaccine Breakthrough Infections, Associated with Large Public Gatherings — Barnstable County, Massachusetts, July 2021. MMWR Morb Mortal Wkly Rep [Internet]. 2021 [cited 2021 Sep 8];70. Available from: https://www.cdc.gov/mmwr/volumes/70/wr/mm7031e2.htm

363. Shamier MC, Tostmann A, Bogers S, Wilde JD, IJpelaar J, Kleij WVD, et al. Virological characteristics of SARS-CoV-2 vaccine breakthrough infections in health care workers [Internet]. 2021 Aug [cited 2021 Aug 23] p. 2021.08.20.21262158. Available from: https://www.medrxiv.org/content/10.1101/2021.08.20.21262158v1

364. Ke R, Martinez P, Smith RL, Gibson L, Achenbach C, McFall S, et al. Longitudinal analysis of SARS-CoV-2 vaccine breakthrough infections reveal limited infectious virus shedding and restricted tissue distribution [Internet]. 2021 Sep [cited 2021 Sep 3] p. 2021.08.30.21262701. Available from: https://www.medrxiv.org/content/10.1101/2021.08.30.21262701v1

365. Kam K, Yung CF, Cui L, Lin Tzer Pin R, Mak TM, Maiwald M, et al. A Well Infant with Coronavirus Disease 2019 (COVID-19) with High Viral Load. Clin Infect Dis [Internet]. [cited 2020 Mar 4]; Available from: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa201/5766416

366. Mizumoto K, Chowell G. Transmission potential of the novel coronavirus (COVID-19) onboard the diamond Princess Cruises Ship, 2020. Infectious Disease Modelling. 2020;5:264–70.

367. Nishiura H, Kobayashi T, Suzuki A, Jung S-M, Hayashi K, Kinoshita R, et al. Estimation of the asymptomatic ratio of novel coronavirus infections (COVID-19). International Journal of Infectious Diseases. 2020 Mar;S1201971220301399.

368. Luo S-H, Liu W, Liu Z-J, Zheng X-Y, Hong C-X, Liu Z-R, et al. A confirmed asymptomatic carrier of 2019 novel coronavirus (SARS-CoV-2). Chinese Medical Journal [Internet]. 2020 Mar 23 [cited 2020 Mar 26];Publish Ahead of Print. Available from: https://journals.lww.com/cmj/Citation/publishahead/A_confirmed_asymptomatic_carrier_of_2019_novel.99353.aspx

369. Kimball A. Asymptomatic and Presymptomatic SARS-CoV-2 Infections in Residents of a Long-Term Care Skilled Nursing Facility — King County, Washington, March 2020. MMWR Morb Mortal

Wkly Rep [Internet]. 2020 [cited 2020 Apr 12];69. Available from: https://www.cdc.gov/mmwr/volumes/69/wr/mm6913e1.htm

370. Hu Z, Song C, Xu C, Jin G, Chen Y, Xu X, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. Sci China Life Sci. 2020 Mar 4;

371. Sutton D, Fuchs K, D'Alton M, Goffman D. Universal Screening for SARS-CoV-2 in Women Admitted for Delivery. New England Journal of Medicine. 2020 Apr 13;0(0):null.

372. Kimball A, Hatfield KM, Arons M, James A, Taylor J, Spicer K, et al. Asymptomatic and Presymptomatic SARS-CoV-2 Infections in Residents of a Long-Term Care Skilled Nursing Facility - King County, Washington, March 2020. MMWR Morb Mortal Wkly Rep. 2020 Apr 3;69(13):377–81.

373. Coronavirus clue? Most cases aboard U.S. aircraft carrier are symptom-free. Reuters [Internet]. 2020 Apr 16 [cited 2020 Apr 18]; Available from: https://www.reuters.com/article/us-health-coronavirus-usa-military-sympt-idUSKCN21Y2GB

374. Meyerowitz EA, Richterman A, Bogoch II, Low N, Cevik M. Towards an accurate and systematic characterisation of persistently asymptomatic infection with SARS-CoV-2. The Lancet Infectious Diseases [Internet]. 2020 Dec 7 [cited 2020 Dec 14];0(0). Available from: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30837-9/abstract

375. Buitrago-Garcia D, Egli-Gany D, Counotte MJ, Hossmann S, Imeri H, Ipekci AM, et al. Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: A living systematic review and meta-analysis. PLOS Medicine. 2020 Sep 22;17(9):e1003346.

376. Byambasuren O, Cardona M, Bell K, Clark J, McLaws M-L, Glasziou P. Estimating the extent of asymptomatic COVID-19 and its potential for community transmission: Systematic review and meta-analysis. Official Journal of the Association of Medical Microbiology and Infectious Disease Canada. 2020 Dec 11;e20200030.

377. Koh WC, Naing L, Chaw L, Rosledzana MA, Alikhan MF, Jamaludin SA, et al. What do we know about SARS-CoV-2 transmission? A systematic review and meta-analysis of the secondary attack rate and associated risk factors. PLOS ONE. 2020 Oct 8;15(10):e0240205.

378. Qiu X, Nergiz AI, Maraolo AE, Bogoch II, Low N, Cevik M. Defining the role of asymptomatic and pre-symptomatic SARS-CoV-2 transmission – a living systematic review. Clinical Microbiology and Infection [Internet]. 2021 Jan 21 [cited 2021 Jan 28]; Available from: http://www.sciencedirect.com/science/article/pii/S1198743X21000380

379. Li F, Li Y-Y, Liu M-J, Fang L-Q, Dean NE, Wong GWK, et al. Household transmission of SARS-CoV-2 and risk factors for susceptibility and infectivity in Wuhan: a retrospective observational study. The Lancet Infectious Diseases [Internet]. 2021 Jan 18 [cited 2021 Jan 25];0(0). Available from: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30981-6/abstract

380. Hippich M, Holthaus L, Assfalg R, Zapardiel-Gonzalo J, Kapfelsperger H, Heigermoser M, et al. A Public Health Antibody Screening Indicates a 6-Fold Higher SARS-CoV-2 Exposure Rate than Reported Cases in Children. Med [Internet]. 2020 Oct 29 [cited 2020 Dec 9]; Available from: http://www.sciencedirect.com/science/article/pii/S2666634020300209

381. Tosif S, Neeland MR, Sutton P, Licciardi PV, Sarkar S, Selva KJ, et al. Immune responses to SARS-CoV-2 in three children of parents with symptomatic COVID-19. Nat Commun. 2020 11;11(1):5703.

382. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. 2020 Mar;S0140673620305663.

383. Jin Y-H, Zhan Q-Y, Peng Z-Y, Ren X-Q, Yin X-T, Cai L, et al. Chemoprophylaxis, diagnosis, treatments, and discharge management of COVID-19: An evidence-based clinical practice guideline (updated version). Mil Med Res. 2020 Sep 4;7(1):41–41.

384. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol [Internet]. 2020 Apr 10 [cited 2020 Apr 13]; Available from: https://jamanetwork.com/journals/jamaneurology/fullarticle/2764549

385. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun. 2020 Mar 30;

386. Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. Journal of the European Academy of Dermatology and Venereology [Internet]. [cited 2020 Apr 16];n/a(n/a). Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/jdv.16387

387. Atri D, Siddiqi HK, Lang J, Nauffal V, Morrow DA, Bohula EA. COVID-19 for the Cardiologist: A Current Review of the Virology, Clinical Epidemiology, Cardiac and Other Clinical Manifestations and Potential Therapeutic Strategies. JACC Basic Transl Sci. 2020 Apr 10;

388. Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol. 2020 Apr 6;

389. Yan CH, Faraji F, Prajapati DP, Boone CE, DeConde AS. Association of chemosensory dysfunction and Covid-19 in patients presenting with influenza-like symptoms. Int Forum Allergy Rhinol. 2020 Apr 12;

390. Suzuki M, Saito K, Min W-P, Vladau C, Toida K, Itoh H, et al. Identification of viruses in patients with postviral olfactory dysfunction. Laryngoscope. 2007 Feb;117(2):272–7.

391. Hoang MP, Kanjanaumporn J, Aeumjaturapat S, Chusakul S, Seresirikachorn K, Snidvongs K. Olfactory and gustatory dysfunctions in COVID-19 patients: A systematic review and meta-analysis. Asian Pac J Allergy Immunol. 2020 Jun 21;

392. Team TNCPERE. The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) — China, 2020. CCDCW. 2020 Feb 1;2:1–10.

393. Rocke J, Hopkins C, Philpott C, Kumar N. Is loss of sense of smell a diagnostic marker in COVID-19: A systematic review and meta-analysis. Clin Otolaryngol. 2020 Aug 1;

394. Tostmann A, Bradley J, Bousema T, Yiek W-K, Holwerda M, Bleeker-Rovers C, et al. Strong associations and moderate predictive value of early symptoms for SARS-CoV-2 test positivity among healthcare workers, the Netherlands, March 2020. Euro Surveill. 2020 Apr;25(16).

395. Roland LT, Gurrola JG 2nd, Loftus PA, Cheung SW, Chang JL. Smell and taste symptom-based predictive model for COVID-19 diagnosis. Int Forum Allergy Rhinol. 2020 Jul;10(7):832–8.

396. Lan F-Y, Filler R, Mathew S, Buley J, Iliaki E, Bruno-Murtha LA, et al. COVID-19 symptoms predictive of healthcare workers' SARS-CoV-2 PCR results. PLoS One. 2020;15(6):e0235460.

397. Menni C, Valdes AM, Freidin MB, Sudre CH, Nguyen LH, Drew DA, et al. Real-time tracking of self-reported symptoms to predict potential COVID-19. Nat Med. 2020 Jul;26(7):1037–40.

398. Deng Y, Liu W, Liu K, Fang Y-Y, Shang J, Zhou L, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study. Chin Med J. 2020 Mar 20;

399. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. The Lancet Respiratory Medicine [Internet]. 2020 Feb 24 [cited 2020 Mar 2];0(0). Available from: https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30079-5/abstract

400. Xie J, Tong Z, Guan X, Du B, Qiu H, Slutsky AS. Critical care crisis and some recommendations during the COVID-19 epidemic in China. Intensive Care Med. 2020 May 1;46(5):837–40.

401. Ottestad W, Seim M, Mæhlen JO. COVID-19 with silent hypoxemia. Tidsskrift for Den norske legeforening [Internet]. 2020 Apr 21 [cited 2020 May 18]; Available from: https://tidsskriftet.no/en/2020/04/kort-kasuistikk/covid-19-silent-hypoxemia

402. Wilkerson RG, Adler JD, Shah NG, Brown R. Silent hypoxia: A harbinger of clinical deterioration in patients with COVID-19. Am J Emerg Med. 2020 May 22;

403. Xie Y, Wang X, Yang P, Zhang S. COVID-19 Complicated by Acute Pulmonary Embolism. Radiology: Cardiothoracic Imaging. 2020 Mar 16;2(2):e200067.

404. Chen J, Wang X, Zhang S, Liu B, Wu X, Wang Y, et al. Findings of Acute Pulmonary Embolism in COVID-19 Patients [Internet]. Rochester, NY: Social Science Research Network; 2020 Mar [cited 2020 Apr 6]. Report No.: ID 3548771. Available from: https://papers.ssrn.com/abstract=3548771

405. Traitement anticoagulant pour la prévention du risque thrombotique chez un patient hospitalisé avec Covid-19 et surveillance de l'hémostase - La SFAR [Internet]. Société Française d'Anesthésie et de Réanimation. 2020 [cited 2020 Apr 4]. Available from: https://sfar.org/traitement-anticoagulant-pour-la-prevention-du-risque-thrombotique-chez-un-patient-hospitalise-avec-covid-19-et-surveillance-de-lhemostase/

406. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thrombosis Research. 2020 Apr;S0049384820301201.

407. Rapid risk assessment: Coronavirus disease 2019 (COVID-19) pandemic: increased transmission in the EU/EEA and the UK – seventh update [Internet]. European Centre for Disease Prevention and Control. 2020 [cited 2020 Mar 26]. Available from: https://www.ecdc.europa.eu/en/publications-data/rapid-risk-assessment-coronavirus-disease-2019-covid-19-pandemic

408. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA [Internet]. 2020 Apr 6 [cited 2020 Apr 7]; Available from: https://doi.org/10.1001/jama.2020.5394

409. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 2020 Aug 25;324(8):782–93.

410. Pastor-Barriuso R, Pérez-Gómez B, Hernán MA, Pérez-Olmeda M, Yotti R, Oteo-Iglesias J, et al. Infection fatality risk for SARS-CoV-2 in community dwelling population of Spain: nationwide seroepidemiological study. BMJ [Internet]. 2020 Nov 27 [cited 2020 Dec 1];371. Available from: https://www.bmj.com/content/371/bmj.m4509

411. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nature Medicine. 2021 Mar 22;1–15.

412. CDC. COVID-19 and Your Health [Internet]. Centers for Disease Control and Prevention. 2020 [cited 2020 Dec 28]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/faq.html

413. In the wake of the pandemic: preparing for Long COVID (2021) [Internet]. [cited 2021 May 10]. Available from: https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/publications-and-technical-guidance/2021/in-the-wake-of-the-pandemic-preparing-for-long-covid-2021

414. Castanares-Zapatero D, Chalon P. Pathophysiology of Long COVID: a preliminary report. :56.

415. Needs and follow-up of long-term Covid-19 patients (ongoing study) [Internet]. [cited 2021 May 24]. Available from: /en/needs-and-follow-up-of-long-term-covid-19-patients-ongoing-study

416. The prevalence of long COVID symptoms and COVID-19 complications - Office for National Statistics [Internet]. [cited 2021 May 9]. Available from: https://www.ons.gov.uk/news/statementsandletters/theprevalenceoflongcovidsymptomsandcovid19complications

417. Long COVID: What do we know so far? [Internet]. [cited 2021 May 24]. Available from: https://covid.joinzoe.com/post/long-covid-what-we-know

418. Havervall S, Rosell A, Phillipson M, Mangsbo SM, Nilsson P, Hober S, et al. Symptoms and Functional Impairment Assessed 8 Months After Mild COVID-19 Among Health Care Workers. JAMA [Internet]. 2021 Apr 7 [cited 2021 May 9]; Available from: https://jamanetwork.com/journals/jama/fullarticle/2778528

419. Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, et al. Attributes and predictors of long COVID. Nat Med. 2021 Apr;27(4):626–31.

420. Ludvigsson JF. Case report and systematic review suggest that children may experience similar long-term effects to adults after clinical COVID-19. Acta Paediatr [Internet]. 2020 Dec 3 [cited 2021 May 24]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7753397/

421. Yelin D, Wirtheim E, Vetter P, Kalil AC, Bruchfeld J, Runold M, et al. Long-term consequences of COVID-19: research needs. The Lancet Infectious Diseases. 2020;20(10):1115–7.

422. Dennis A, Wamil M, Kapur S, Alberts J, Badley AD, Decker GA, et al. Multi-organ impairment in low-risk individuals with long COVID. medRxiv. 2020 Oct 16;2020.10.14.20212555.

423. Rubino F, Amiel SA, Zimmet P, Alberti G, Bornstein S, Eckel RH, et al. New-Onset Diabetes in Covid-19. The New England Journal of Medicine. 2020 20;383(8):789–90.

424. Salehi S, Reddy S, Gholamrezanezhad A. Long-term Pulmonary Consequences of Coronavirus Disease 2019 (COVID-19): What We Know and What to Expect. Journal of Thoracic Imaging. 2020 Jul;35(4):W87–9.

425. Zhao Y-M, Shang Y-M, Song W-B, Li Q-Q, Xie H, Xu Q-F, et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. EClinicalMedicine. 2020 Aug;25:100463.

426. Kinaret PAS, Del Giudice G, Greco D. Covid-19 acute responses and possible long term consequences: What nanotoxicology can teach us. Nano Today. 2020 Dec;35:100945.

427. Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). JAMA cardiology. 2020 Jul 27;

428. Becker RC. Anticipating the long-term cardiovascular effects of COVID-19. Journal of Thrombosis and Thrombolysis. 2020 Oct;50(3):512–24.

429. Iadecola C, Anrather J, Kamel H. Effects of COVID-19 on the Nervous System. Cell. 2020 Oct 1;183(1):16-27.e1.

430. Abate G, Memo M, Uberti D. Impact of COVID-19 on Alzheimer's Disease Risk: Viewpoint for Research Action. Healthcare (Basel, Switzerland). 2020 Aug 21;8(3).

431. Lennon JC. Neurologic and Immunologic Complications of COVID-19: Potential Long-Term Risk Factors for Alzheimer's Disease. Journal of Alzheimer's Disease Reports. 2020 Jun 16;4(1):217–21.

432. Troyer EA, Kohn JN, Hong S. Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. Brain Behav Immun. 2020 Apr 13;

433. Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. The Lancet Psychiatry. 2021 May 1;8(5):416–27.

434. Ziauddeen N, Gurdasani D, O'Hara ME, Hastie C, Roderick P, Yao G, et al. Characteristics of Long Covid: findings from a social media survey [Internet]. 2021 Mar [cited 2021 Aug 31] p. 2021.03.21.21253968. Available from: https://www.medrxiv.org/content/10.1101/2021.03.21.21253968v2

435. Clinical characteristics of COVID-19 [Internet]. European Centre for Disease Prevention and Control. [cited 2021 Aug 31]. Available from: https://www.ecdc.europa.eu/en/covid-19/latest-evidence/clinical

436. COVID-19 rapid guideline: managing the long-term effects of COVID-19. :35.

437. Perrin R, Riste L, Hann M, Walther A, Mukherjee A, Heald A. Into the looking glass: Post-viral syndrome post COVID-19. Medical Hypotheses. 2020 Jun 27;144:110055.

438. Laëtitia LG. Réponses rapides dans le cadre de la Covid-19 : Symptômes prolongés suite à une Covid-19 de l'adulte - Diagnostic et prise en charge. 2021;27.

439. Rockx B, Kuiken T, Herfst S, Bestebroer T, Lamers MM, Munnink BBO, et al. Comparative pathogenesis of COVID-19, MERS, and SARS in a nonhuman primate model. Science [Internet]. 2020 Apr 17 [cited 2020 Apr 19]; Available from: https://science.sciencemag.org/content/early/2020/04/16/science.abb7314

440. Liu Y, Yan L-M, Wan L, Xiang T-X, Le A, Liu J-M, et al. Viral dynamics in mild and severe cases of COVID-19. The Lancet Infectious Diseases [Internet]. 2020 Mar 19 [cited 2020 Mar 25]; Available from: http://www.sciencedirect.com/science/article/pii/S1473309920302322

441. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. Journal of Infection [Internet]. 2020 Apr 10 [cited 2020 Apr 20]; Available from: http://www.sciencedirect.com/science/article/pii/S0163445320301651

442. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. The Lancet Respiratory Medicine. 2020 Apr 1;8(4):420–2.

443. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 2020 Feb;395(10223):497–506.

444. [Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia]. - Abstract - Europe PMC [Internet]. [cited 2020 Apr 20]. Available from: https://europepmc.org/article/med/32026671

445. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. The Lancet. 2020 May 2;395(10234):1417–8.

446. Zhang Y, Cao W, Xiao M, Li YJ, Yang Y, Zhao J, et al. [Clinical and coagulation characteristics of 7 patients with critical COVID-2019 pneumonia and acro-ischemia]. Zhonghua Xue Ye Xue Za Zhi. 2020 Mar 28;41(0):E006.

447. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. Journal of Thrombosis and Haemostasis. 2020;18(4):844–7.

448. Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. Transl Res. 2020 Apr 15;

449. Tetro JA. Is COVID-19 receiving ADE from other coronaviruses? Microbes and Infection. 2020 Mar 1;22(2):72–3.

450. Tilocca B, Soggiu A, Musella V, Britti D, Sanguinetti M, Urbani A, et al. Molecular basis of COVID-19 relationships in different species: a one health perspective. Microbes Infect. 2020 Mar 17;

451. Du L, He Y, Zhou Y, Liu S, Zheng B-J, Jiang S. The spike protein of SARS-CoV — a target for vaccine and therapeutic development. Nature Reviews Microbiology. 2009 Mar;7(3):226–36.

452. Longitudinal evaluation and decline of antibody responses in SARS-CoV-2 infection | medRxiv [Internet]. [cited 2020 Sep 9]. Available from: https://www.medrxiv.org/content/10.1101/2020.07.09.20148429v1

453. Long Q-X, Tang X-J, Shi Q-L, Li Q, Deng H-J, Yuan J, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nat Med [Internet]. 2020 Jun 18 [cited 2020 Jun 22]; Available from: http://www.nature.com/articles/s41591-020-0965-6

454. Rapid Decay of Anti–SARS-CoV-2 Antibodies in Persons with Mild Covid-19 [Internet]. [cited 2020 Sep 9]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7397184/

455. Gudbjartsson DF, Norddahl GL, Melsted P, Gunnarsdottir K, Holm H, Eythorsson E, et al. Humoral Immune Response to SARS-CoV-2 in Iceland. New England Journal of Medicine. 2020 Sep 1;0(0):null.

456. Gallais F, Gantner P, Bruel T, Velay A, Planas D, Wendling M-J, et al. Evolution of antibody responses up to 13 months after SARS-CoV-2 infection and risk of reinfection. EBioMedicine. 2021 Sep 1;71:103561.

457. Havervall S, Ng H, Falk AJ, Greilert-Norin N, Månberg A, Marking U, et al. Robust humoral and cellular immune responses and low risk for reinfection at least eight months following asymptomatic to mild COVID-19. Journal of Internal Medicine [Internet]. [cited 2021 Sep 9];n/a(n/a). Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/joim.13387

458. Wang Z, Muecksch F, Schaefer-Babajew D, Finkin S, Viant C, Gaebler C, et al. Naturally enhanced neutralizing breadth against SARS-CoV-2 one year after infection. Nature. 2021 Jul;595(7867):426–31.

459. Pannus P, Neven KY, Craeye SD, Heyndrickx L, Kerckhove SV, Georges D, et al. Poor antibody response to BioNTech/Pfizer COVID-19 vaccination in SARS-CoV-2 naïve residents of nursing homes [Internet]. 2021 Jun [cited 2021 Sep 10] p. 2021.06.08.21258366. Available from: https://www.medrxiv.org/content/10.1101/2021.06.08.21258366v1

460. Brouwer PJM, Caniels TG, van der Straten K, Snitselaar JL, Aldon Y, Bangaru S, et al. Potent neutralizing antibodies from COVID-19 patients define multiple targets of vulnerability. Science. 2020 07;369(6504):643–50.

461. Rogers TF, Zhao F, Huang D, Beutler N, Burns A, He W-T, et al. Isolation of potent SARS-CoV-2 neutralizing antibodies and protection from disease in a small animal model. Science. 2020 21;369(6506):956–63.

462. Lack of Reinfection in Rhesus Macaques Infected with SARS-CoV-2 | bioRxiv [Internet]. [cited 2020 May 11]. Available from: https://www.biorxiv.org/content/10.1101/2020.03.13.990226v2

463. Wu F, Wang A, Liu M, Wang Q, Chen J, Xia S, et al. Neutralizing Antibody Responses to SARS-CoV-2 in a COVID-19 Recovered Patient Cohort and Their Implications [Internet]. Rochester, NY: Social Science Research Network; 2020 Mar [cited 2020 May 11]. Report No.: ID 3566211. Available from: https://papers.ssrn.com/abstract=3566211

464. Yuchun N, Guangwen W, Xuanling S, Hong Z, Yan Q, Zhongping H, et al. Neutralizing Antibodies in Patients with Severe Acute Respiratory Syndrome-Associated Coronavirus Infection. J Infect Dis. 2004 Sep 15;190(6):1119–26.

465. Guo X, Guo Z, Duan C, Chen Z, Wang G, Lu Y, et al. Long-Term Persistence of IgG Antibodies in SARS-CoV Infected Healthcare Workers. medRxiv. 2020 Feb 14;2020.02.12.20021386.

466. Choe PG, Perera R a. PM, Park WB, Song K-H, Bang JH, Kim ES, et al. MERS-CoV Antibody Responses 1 Year after Symptom Onset, South Korea, 2015. Emerging Infect Dis. 2017;23(7):1079–84.

467. Galanti M, Shaman J. Direct observation of repeated infections with endemic coronaviruses [Internet]. Infectious Diseases (except HIV/AIDS); 2020 May [cited 2020 May 11]. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.04.27.20082032

468. Sekine T, Perez-Potti A, Rivera-Ballesteros O, Strålin K, Gorin J-B, Olsson A, et al. Robust T cell immunity in convalescent individuals with asymptomatic or mild COVID-19. Cell [Internet]. 2020 Aug 14 [cited 2020 Sep 9]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7427556/

469. Peng Y, Mentzer AJ, Liu G, Yao X, Yin Z, Dong D, et al. Broad and strong memory CD4+ and CD8+ T cells induced by SARS-CoV-2 in UK convalescent individuals following COVID-19. Nat Immunol. 2020;21(11):1336–45.

470. Le Bert N, Tan AT, Kunasegaran K, Tham CYL, Hafezi M, Chia A, et al. SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls. Nature. 2020;584(7821):457–62.

471. Kroemer M, Spehner L, Vettoretti L, Bouard A, Eberst G, Pili Floury S, et al. COVID-19 patients display distinct SARS-CoV-2 specific T-cell responses according to disease severity. J Infect. 2020 Aug 25;4816.

472. Nelde A, Bilich T, Heitmann JS, Maringer Y, Salih HR, Roerden M, et al. SARS-CoV-2-derived peptides define heterologous and COVID-19-induced T cell recognition. Nat Immunol. 2020 Sep 30;

473. Schulien I, Kemming J, Oberhardt V, Wild K, Seidel LM, Killmer S, et al. Ex vivo detection of SARS-CoV-2-specific CD8+ T cells: rapid induction, prolonged contraction, and formation of functional memory. bioRxiv. 2020 Jan 1;2020.08.13.249433.

474. Weiskopf D, Schmitz KS, Raadsen MP, Grifoni A, Okba NMA, Endeman H, et al. Phenotype and kinetics of SARS-CoV-2-specific T cells in COVID-19 patients with acute respiratory distress syndrome. Sci Immunol. 2020 26;5(48).

475. Grifoni A, Weiskopf D, Ramirez SI, Mateus J, Dan JM, Moderbacher CR, et al. Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals. Cell. 2020 25;181(7):1489-1501.e15.

476. Braun J, Loyal L, Frentsch M, Wendisch D, Georg P, Kurth F, et al. SARS-CoV-2-reactive T cells in healthy donors and patients with COVID-19. Nature. 2020 Jul 29;

477. Zhang F, Gan R, Zhen Z, Hu X, Li X, Zhou F, et al. Adaptive immune responses to SARS-CoV-2 infection in severe versus mild individuals. Signal Transduct Target Ther. 2020 14;5(1):156.

478. Gallais F, Velay A, Wendling M-J, Nazon C, Partisani M, Sibilia J, et al. Intrafamilial Exposure to SARS-CoV-2 Induces Cellular Immune Response without Seroconversion. medRxiv. 2020 Jun 22;2020.06.21.20132449.

479. Rydyznski Moderbacher C, Ramirez SI, Dan JM, Grifoni A, Hastie KM, Weiskopf D, et al. Antigen-Specific Adaptive Immunity to SARS-CoV-2 in Acute COVID-19 and Associations with Age and Disease Severity. Cell. 2020 Nov 12;183(4):996-1012.e19.

480. Woldemeskel BA, Kwaa AK, Garliss CC, Laeyendecker O, Ray SC, Blankson JN. Healthy donor T-cell responses to common cold coronaviruses and SARS-CoV-2. J Clin Invest. 2020 Sep 23;

481. Tang F, Quan Y, Xin Z-T, Wrammert J, Ma M-J, Lv H, et al. Lack of peripheral memory B cell responses in recovered patients with severe acute respiratory syndrome: a six-year follow-up study. J Immunol. 2011 Jun 15;186(12):7264–8.

482. Tan Y, Liu F, Xu X, Ling Y, Huang W, Zhu Z, et al. Durability of neutralizing antibodies and T-cell response post SARS-CoV-2 infection. Front Med. 2020 Oct 5;

483. Neidleman J, Luo X, Frouard J, Xie G, Gill G, Stein ES, et al. SARS-CoV-2-Specific T Cells Exhibit Phenotypic Features of Helper Function, Lack of Terminal Differentiation, and High Proliferation Potential. Cell Rep Med. 2020 Sep 22;1(6):100081.

484. Dan JM, Mateus J, Kato Y, Hastie KM, Yu ED, Faliti CE, et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. Science. 2021 Feb 5;371(6529):eabf4063.

485. Cromer D, Juno JA, Khoury D, Reynaldi A, Wheatley AK, Kent SJ, et al. Prospects for durable immune control of SARS-CoV-2 and prevention of reinfection. Nat Rev Immunol. 2021 Apr 29;1–10.

486. Gaebler C, Wang Z, Lorenzi JCC, Muecksch F, Finkin S, Tokuyama M, et al. Evolution of antibody immunity to SARS-CoV-2. Nature. 2021 Mar;591(7851):639–44.

487. Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat Med. 2021 Jul;27(7):1205–11.

488. To KK-W, Hung IF-N, Ip JD, Chu AW-H, Chan W-M, Tam AR, et al. COVID-19 re-infection by a phylogenetically distinct SARS-coronavirus-2 strain confirmed by whole genome sequencing. Clin Infect Dis [Internet]. [cited 2020 Aug 28]; Available from: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1275/5897019

489. Tillett RL, Sevinsky JR, Hartley PD, Kerwin H, Crawford N, Gorzalski A, et al. Genomic evidence for reinfection with SARS-CoV-2: a case study. The Lancet Infectious Diseases. 2020 Oct;S1473309920307647.

490. Van Elslande J, Vermeersch P, Vandervoort K, Wawina-Bokalanga T, Vanmechelen B, Wollants E, et al. Symptomatic SARS-CoV-2 reinfection by a phylogenetically distinct strain. Clin Infect Dis [Internet]. [cited 2020 Sep 17]; Available from: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1330/5901661

491. Gupta V, Bhoyar RC, Jain A, Srivastava S, Upadhayay R, Imran M, et al. Asymptomatic reinfection in two healthcare workers from India with genetically distinct SARS-CoV-2. Clin Infect Dis [Internet]. [cited 2020 Oct 7]; Available from: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1451/5910388

492. Prado-Vivar B, Becerra-Wong M, Guadalupe JJ, Marquez S, Gutierrez B, Rojas-Silva P, et al. COVID-19 Re-Infection by a Phylogenetically Distinct SARS-CoV-2 Variant, First Confirmed Event in South America. [Internet]. Rochester, NY: Social Science Research Network; 2020 Sep [cited 2020 Sep 9]. Report No.: ID 3686174. Available from: https://papers.ssrn.com/abstract=3686174

493. Selhorst P, Ierssel SV, Michiels J, Mariën J, Dirinck E, Vandamme S, et al. 1 Symptomatic SARS-CoV-2 re-infection of a health care worker in a 2 Belgian nosocomial outbreak despite primary neutralizing antibody 3 response. :24.

494. Genomic Evidence for a Case of Reinfection with SARS-CoV-2 by Richard Tillett, Joel Sevinsky, Paul Hartley, Heather Kerwin, Natalie Crawford, Andrew Gorzalski, Christopher Laverdure, Subhash Verma, Cyprian Rossetto, David Jackson, Megan Farrell, Stephanie Van Hooser, Mark Pandori :: SSRN [Internet]. [cited 2020 Sep 3]. Available from: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3680955&download=yes

495. To KK-W, Hung IF-N, Chan K-H, Yuan S, To W-K, Tsang DN-C, et al. Serum antibody profile of a patient with COVID-19 reinfection. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America. 2020 Sep 23;

496. Ali AM, Ali KM, Fatah MH, Tawfeeq HM, Rostam HM. SARS-CoV-2 Reinfection in Patients Negative for Immunoglobulin G Following Recovery from COVID-19. medRxiv. 2020 Nov 23;2020.11.20.20234385.

497. Hansen CH, Michlmayr D, Gubbels SM, Mølbak K, Ethelberg S. Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study. The Lancet [Internet]. 2021 Mar 17 [cited 2021 Mar 18];0(0). Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00575-4/abstract

498. Schuler CF, Gherasim C, O'Shea K, Manthei DM, Chen J, Zettel C, et al. Mild SARS-CoV-2 Illness Is Not Associated with Reinfections and Provides Persistent Spike, Nucleocapsid, and Virus-Neutralizing Antibodies. Microbiology Spectrum. 0(0):e00087-21.

499. Hall V, Foulkes S, Charlett A, Atti A, Monk EJM, Simmons R, et al. Do antibody positive healthcare workers have lower SARS-CoV-2 infection rates than antibody negative healthcare workers? Large multi-centre prospective cohort study (the SIREN study), England: June to November 2020. medRxiv. 2021 Jan 15;2021.01.13.21249642.

500. Lumley SF, O'Donnell D, Stoesser NE, Matthews PC, Howarth A, Hatch SB, et al. Antibody Status and Incidence of SARS-CoV-2 Infection in Health Care Workers. New England Journal of Medicine. 2020 Dec 23;0(0):null.

501. Mack CD, Tai C, Sikka R, Grad YH, Maragakis LL, Grubaugh ND, et al. SARS-CoV-2 Reinfection: A Case Series from a 12-Month Longitudinal Occupational Cohort. Clin Infect Dis. 2021 Aug 28;ciab738.

502. Sheehan MM, Reddy AJ, Rothberg MB. Reinfection Rates among Patients who Previously Tested Positive for COVID-19: a Retrospective Cohort Study. Clinical Infectious Diseases [Internet]. 2021 Mar 15 [cited 2021 Mar 18];(ciab234). Available from: https://doi.org/10.1093/cid/ciab234

503. Leidi A, Koegler F, Dumont R, Dubos R, Zaballa M-E, Piumatti G, et al. Risk of reinfection after seroconversion to SARS-CoV-2: A population-based propensity-score matched cohort study. Clinical Infectious Diseases [Internet]. 2021 May 27 [cited 2021 Jun 9];(ciab495). Available from: https://doi.org/10.1093/cid/ciab495

504. Vitale J, Mumoli N, Clerici P, De Paschale M, Evangelista I, Cei M, et al. Assessment of SARS-CoV-2 Reinfection 1 Year After Primary Infection in a Population in Lombardy, Italy. JAMA Intern Med [Internet]. 2021 May 28 [cited 2021 Jun 9]; Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2780557

505. Li J, Zhang L, Liu B, Song D. Case Report: Viral Shedding for 60 Days in a Woman with Novel Coronavirus Disease (COVID-19). Am J Trop Med Hyg. 2020 Apr 27;

506. Molina LP, Chow S-K, Nickel A, Love JE. Prolonged Detection of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) RNA in an Obstetric Patient With Antibody Seroconversion. Obstetrics & Gynecology [Internet]. 2020 Sep 10 [cited 2020 Sep 18];Publish Ahead of Print. Available from: https://journals.lww.com/greenjournal/Abstract/9000/Prolonged_Detection_of_Severe_Acute_Respiratory.97292.aspx

507. Lu J, Peng J, Xiong Q, Liu Z, Lin H, Tan X, et al. Clinical, immunological and virological characterization of COVID-19 patients that test re-positive for SARS-CoV-2 by RT-PCR. EBioMedicine. 2020 Sep;59:102960.

508. Yuan B, Liu H-Q, Yang Z-R, Chen Y-X, Liu Z-Y, Zhang K, et al. Recurrence of positive SARS-CoV-2 viral RNA in recovered COVID-19 patients during medical isolation observation. Sci Rep. 2020 Dec;10(1):11887.

509. Long Q-X, Tang X-J, Shi Q-L, Li Q, Deng H-J, Yuan J, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nature Medicine. 2020 Aug;26(8):1200–4.

510. Cevik M, Tate M, Lloyd O, Maraolo AE, Schafers J, Ho A. SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. The Lancet Microbe [Internet]. 2020 Nov 19 [cited 2020 Nov 23];0(0). Available from: https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(20)30172-5/abstract

511. KCDC. Findings from investigation and analysis of re-positive cases [Internet]. [cited 2020 Jun 11]. Available from: https://is.cdc.go.kr/upload_comm/syview/doc.html?fn=158993708884700.pdf&rs=/upload_comm/docu/0030/

512. Vibholm LK, Nielsen SSF, Pahus MH, Frattari GS, Olesen R, Andersen R, et al. SARS-CoV-2 persistence is associated with antigen-specific CD8 T-cell responses. EBioMedicine. 2021 Feb;64:103230.

513. Zhang Z-L, Hou Y-L, Li D-T, Li F-Z. Laboratory findings of COVID-19: a systematic review and meta-analysis. Scandinavian Journal of Clinical and Laboratory Investigation. 2020 Oct 1;80(6):441–7.

514. Kucirka LM, Lauer SA, Laeyendecker O, Boon D, Lessler J. Variation in False-Negative Rate of Reverse Transcriptase Polymerase Chain Reaction-Based SARS-CoV-2 Tests by Time Since Exposure. Ann Intern Med. 2020 18;173(4):262–7.

515. Mallett S, Allen AJ, Graziadio S, Taylor SA, Sakai NS, Green K, et al. At what times during infection is SARS-CoV-2 detectable and no longer detectable using RT-PCR-based tests? A systematic review of individual participant data. BMC Med. 2020 Nov 4;18(1):346.

516. Yang Y, Yang M, Shen C, Wang F, Yuan J, Li J, et al. Evaluating the accuracy of different respiratory specimens in the laboratory diagnosis and monitoring the viral shedding of 2019-nCoV infections [Internet]. Infectious Diseases (except HIV/AIDS); 2020 Feb [cited 2020 Apr 17]. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.02.11.20021493

517. Tsang NNY, So HC, Ng KY, Cowling BJ, Leung GM, Ip DKM. Diagnostic performance of different sampling approaches for SARS-CoV-2 RT-PCR testing: a systematic review and meta-analysis. Lancet Infect Dis. 2021 Apr 12;

518. Nalla AK, Casto AM, Huang M-LW, Perchetti GA, Sampoleo R, Shrestha L, et al. Comparative Performance of SARS-CoV-2 Detection Assays using Seven Different Primer/Probe Sets and One Assay Kit. J Clin Microbiol. 2020 Apr 8;

519. Wang X, Yao H, Xu X, Zhang P, Zhang M, Shao J, et al. Limits of Detection of Six Approved RT-PCR Kits for the Novel SARS-coronavirus-2 (SARS-CoV-2). Clin Chem. 2020 Apr 13;

520. Population-wide testing of SARS-CoV-2: country experiences and potential approaches in the EU/EEA and the UK. :12.

521. Covid L. ACCELERATED EMERGENCY USE AUTHORIZATION (EUA) SUMMARY COVID-19 RT-PCR TEST (LABORATORY CORPORATION OF AMERICA). :9.

522. Dinnes J, Deeks JJ, Berhane S, Taylor M, Adriano A, Davenport C, et al. Rapid, point-of-care antigen and molecular-based tests for diagnosis of SARS-CoV-2 infection. Cochrane Database of Systematic Reviews [Internet]. 2021 [cited 2021 Apr 15];(3). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013705.pub2/full

523. Poole S, Brendish NJ, Clark TW. SARS-CoV-2 has displaced other seasonal respiratory viruses: Results from a prospective cohort study. Journal of Infection. 2020 Nov;S0163445320307076.

524. Nickbakhsh S, Mair C, Matthews L, Reeve R, Johnson PCD, Thorburn F. Virus–virus interactions impact the population dynamics of influenza and the common cold. 2019 Dec 26;9.

525. Marriott D, Beresford R, Mirdad F, Stark D, Glanville A, Chapman S, et al. Concomitant marked decline in prevalence of SARS-CoV-2 and other respiratory viruses among symptomatic patients following public health interventions in Australia: data from St Vincent's Hospital and associated screening clinics, Sydney, NSW. Clin Infect Dis [Internet]. 2020 Aug 25 [cited 2020 Dec 3]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7499558/

526. Zhang K, Misra A, Kim PJ, Moghadas SM, Langley JM, Smieja M. Rapid disappearance of influenza following the implementation of COVID-19 mitigation measures in Hamilton, Ontario. medRxiv. 2020 Nov 30;2020.11.27.20240036.

527. Haddadin Z, Schuster JE, Spieker AJ, Rahman H, Blozinski A, Stewart L, et al. Acute Respiratory Illnesses in Children in the SARS-CoV-2 Pandemic: Prospective Multicenter Study. Pediatrics. 2021 Aug;148(2):e2021051462.

528. Sberna G, Amendola A, Valli MB, Carletti F, Capobianchi MR, Bordi L, et al. Trend of respiratory pathogens during the COVID-19 epidemic. J Clin Virol. 2020;129:104470.

529. Wee LE, Ko KKK, Ho WQ, Kwek GTC, Tan TT, Wijaya L. Community-acquired viral respiratory infections amongst hospitalized inpatients during a COVID-19 outbreak in Singapore: co-infection and clinical outcomes. J Clin Virol. 2020;128:104436.

530. Leuzinger K, Roloff T, Gosert R, Sogaard K, Naegele K, Rentsch K, et al. Epidemiology of Severe Acute Respiratory Syndrome Coronavirus 2 Emergence Amidst Community-Acquired Respiratory Viruses. J Infect Dis [Internet]. 2020 Jul 29 [cited 2020 Dec 3]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7454752/

531. Lai C-C, Wang C-Y, Hsueh P-R. Co-infections among patients with COVID-19: The need for combination therapy with non-anti-SARS-CoV-2 agents? J Microbiol Immunol Infect. 2020 Aug;53(4):505–12.

532. Stowe J, Tessier E, Zhao H, Guy R, Muller-Pebody B, Zambon M, et al. Interactions between SARS-CoV-2 and Influenza and the impact of coinfection on disease severity: A test negative design. medRxiv. 2020 Sep 22;2020.09.18.20189647.

533. Abduljalil JM. Laboratory diagnosis of SARS-CoV-2: available approaches and limitations. New Microbes New Infect. 2020 Jul;36:100713.

534. Yan Y, Chang L, Wang L. Laboratory testing of SARS-CoV, MERS-CoV, and SARS-CoV-2 (2019-nCoV): Current status, challenges, and countermeasures. Rev Med Virol. 2020 May;30(3):e2106.

535. Infectious Diseases Society of America Guidelines on the Diagnosis of COVID-19 [Internet]. [cited 2021 Apr 7]. Available from: https://www.idsociety.org/practice-guideline/covid-19-guideline-diagnostics/

536. Medeiros da Silva RC, Nogueira Marinho LC, Neto de Araújo Silva D, Costa de Lima K, Pirih FQ, Luz de Aquino Martins AR. Saliva as a possible tool for the SARS-CoV-2 detection: a review. Travel Med Infect Dis [Internet]. 2020 Nov 19 [cited 2020 Nov 24]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7674016/

537. Lee RA, Herigon JC, Benedetti A, Pollock NR, Denkinger CM. Performance of Saliva, Oropharyngeal Swabs, and Nasal Swabs for SARS-CoV-2 Molecular Detection: A Systematic Review and Meta-analysis. medRxiv. 2020 Nov 13;2020.11.12.20230748.

538. Bastos ML, Perlman-Arrow S, Menzies D, Campbell JR. The Sensitivity and Costs of Testing for SARS-CoV-2 Infection With Saliva Versus Nasopharyngeal Swabs : A Systematic Review and Meta-analysis. Ann Intern Med. 2021 Jan 12;

539. Butler-Laporte G, Lawandi A, Schiller I, Yao MC, Dendukuri N, McDonald EG, et al. Comparison of Saliva and Nasopharyngeal Swab Nucleic Acid Amplification Testing for Detection of SARS-CoV-2: A Systematic Review and Meta-analysis. JAMA Intern Med. 2021 Jan 15;

540. Khiabani K, Amirzade-Iranaq MH. Are saliva and deep throat sputum as reliable as common respiratory specimens for SARS-CoV-2 detection? A systematic review and meta-analysis. Am J Infect Control. 2021 Mar 24;

541. Moreira VM, Mascarenhas P, Machado V, Botelho J, Mendes JJ, Taveira N, et al. Diagnosis of SARS-Cov-2 Infection by RT-PCR Using Specimens Other Than Naso- and Oropharyngeal Swabs: A Systematic Review and Meta-Analysis. Diagnostics (Basel). 2021 Feb 21;11(2).

542. Ibrahimi N, Delaunay-Moisan A, Hill C, Teuff GL, Rupprecht J-F, Thuret J-Y, et al. Screening for SARS-CoV-2 by RT-PCR: saliva or nasopharyngeal swab? Systematic review and meta-analysis. medRxiv. 2021 Feb 12;2021.02.10.21251508.

543. Mestdagh P, Gillard M, Arbyn M, Pirnay J-P, Poels J, Hellemans J, et al. Evaluation of saliva sampling procedures for SARS-CoV-2 diagnostics reveals differential sensitivity and association with viral load. medRxiv. 2020 Oct 13;2020.10.06.20207902.

544. Rao M, Rashid FA, Sabri FSAH, Jamil NN, Zain R, Hashim R, et al. Comparing nasopharyngeal swab and early morning saliva for the identification of SARS-CoV-2. Clin Infect Dis. 2020 Aug 6;

545. Hung DL-L, Li X, Chiu KH-Y, Yip CC-Y, To KK-W, Chan JF-W, et al. Early-Morning vs Spot Posterior Oropharyngeal Saliva for Diagnosis of SARS-CoV-2 Infection: Implication of Timing of Specimen Collection for Community-Wide Screening. Open Forum Infect Dis [Internet]. 2020 Jun 1 [cited 2020 Oct 9];7(6). Available from: https://academic.oup.com/ofid/article/7/6/ofaa210/5854323

546. Guest JL, Sullivan PS, Valentine-Graves M, Valencia R, Adam E, Luisi N, et al. Suitability and Sufficiency of Telehealth Clinician-Observed, Participant-Collected Samples for SARS-CoV-2 Testing: The iCollect Cohort Pilot Study. JMIR Public Health Surveill. 2020 25;6(2):e19731.

547. Chen JH-K, Yip CC-Y, Poon RW-S, Chan K-H, Cheng VC-C, Hung IF-N, et al. Evaluating the use of posterior oropharyngeal saliva in a point-of-care assay for the detection of SARS-CoV-2. Emerging Microbes & Infections. 2020 Jan 1;9(1):1356–9.

548. Wong SCY, Tse H, Siu HK, Kwong TS, Chu MY, Yau FYS, et al. Posterior Oropharyngeal Saliva for the Detection of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis [Internet]. 2020 May 13 [cited 2020 Oct 9]; Available from: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa797/5860439

549. Goldfarb DM, Tilley P, Al-Rawahi GN, Srigley JA, Ford G, Pedersen H, et al. Self-collected Saline Gargle Samples as an Alternative to Healthcare Worker Collected Nasopharyngeal Swabs for COVID-19 Diagnosis in Outpatients. J Clin Microbiol. 2021 Jan 29;

550. Fernández-González M, Agulló V, de la Rica A, Infante A, Carvajal M, García JA, et al. Performance of Saliva Specimens for the Molecular Detection of SARS-CoV-2 in the Community Setting: Does Sample Collection Method Matter? J Clin Microbiol. 2021 Mar 19;59(4).

551. Nacher M, Mergeay-Fabre M, Blanchet D, Benoit O, Pozl T, Mesphoule P, et al. Prospective Comparison of Saliva and Nasopharyngeal Swab Sampling for Mass Screening for COVID-19. Front Med (Lausanne). 2021;8:621160.

552. Kernéis S, Elie C, Fourgeaud J, Choupeaux L, Delarue SM, Alby M-L, et al. Accuracy of saliva and nasopharyngeal sampling for detection of SARS-CoV-2 in community screening: a multicentric cohort study. Eur J Clin Microbiol Infect Dis. 2021 Aug 3;

553. Congrave-Wilson Z, Lee Y, Jumarang J, Perez S, Bender JM, Bard JD, et al. Change in Saliva RT-PCR Sensitivity Over the Course of SARS-CoV-2 Infection. JAMA [Internet]. 2021 Aug 13 [cited 2021 Aug 27]; Available from: https://doi.org/10.1001/jama.2021.13967

554. Norizuki M, Hachiya M, Motohashi A, Moriya A, Mezaki K, Kimura M, et al. Effective screening strategies for detection of asymptomatic COVID-19 travelers at airport quarantine stations: Exploratory findings in Japan. Glob Health Med. 2021 Apr 30;3(2):107–11.

555. Revel M-P, Parkar AP, Prosch H, Silva M, Sverzellati N, Gleeson F, et al. COVID-19 patients and the Radiology department – advice from the European Society of Radiology (ESR) and the European Society of Thoracic Imaging (ESTI). 2020;11.

556. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. Radiology. 2020 Feb 26;200642.

557. Xie X, Zhong Z, Zhao W, Zheng C, Wang F, Liu J. Chest CT for Typical 2019-nCoV Pneumonia: Relationship to Negative RT-PCR Testing. Radiology. 2020 Feb 12;200343.

558. Bernheim A, Mei X, Huang M, Yang Y, Fayad ZA, Zhang N, et al. Chest CT Findings in Coronavirus Disease-19 (COVID-19): Relationship to Duration of Infection. Radiology. 2020 Feb 20;200463.

559. Wang Y, Dong C, Hu Y, Li C, Ren Q, Zhang X, et al. Temporal Changes of CT Findings in 90 Patients with COVID-19 Pneumonia: A Longitudinal Study. Radiology. 2020 Mar 19;200843.

560. Inui S, Fujikawa A, Jitsu M, Kunishima N, Watanabe S, Suzuki Y, et al. Chest CT Findings in Cases from the Cruise Ship "Diamond Princess" with Coronavirus Disease 2019 (COVID-19). Radiology: Cardiothoracic Imaging. 2020 Mar 17;2(2):e200110.

561. O'Murchu E. Evidence summary of the immune response following infection with SARS-CoV-2 or other human coronaviruses. :139.

562. Ruetalo N, Businger R, Althaus K, Fink S, Ruoff F, Hamprecht K, et al. Neutralizing antibody response in non-hospitalized SARS-CoV-2 patients. medRxiv [Internet]. 2020; Available from: https://www.medrxiv.org/content/early/2020/08/07/2020.08.07.20169961

563. Röltgen K, Wirz OF, Stevens BA, Powell AE, Hogan CA, Najeeb J, et al. SARS-CoV-2 Antibody Responses Correlate with Resolution of RNAemia But Are Short-Lived in Patients with Mild Illness [Internet]. Infectious Diseases (except HIV/AIDS); 2020 Aug [cited 2020 Sep 18]. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.08.15.20175794

564. GeurtsvanKessel CH, Okba NMA, Igloi Z, Bogers S, Embregts CWE, Laksono BM, et al. An evaluation of COVID-19 serological assays informs future diagnostics and exposure assessment. Nat Commun. 2020 Dec;11(1):3436.

565. Lisboa Bastos M, Tavaziva G, Abidi SK, Campbell JR, Haraoui L-P, Johnston JC, et al. Diagnostic accuracy of serological tests for covid-19: systematic review and meta-analysis. BMJ. 2020 Jul 1;m2516.

566. Guo L, Ren L, Yang S, Xiao M, Chang D, Yang F, et al. Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19). Clin Infect Dis. 2020 Mar 21;

567. Wan WY, Lim SH, Seng EH. Cross-reaction of sera from COVID-19 patients with SARS-CoV assays. medRxiv. 2020 Mar 23;2020.03.17.20034454.

568. Hanson KE, Caliendo AM, Arias CA, Englund JA, Hayden MK, Lee MJ, et al. Infectious Diseases Society of America Guidelines on the Diagnosis of COVID-19:Serologic Testing. Clinical Infectious Diseases. 2020 Sep 12;ciaa1343.

569. openFDA [Internet]. [cited 2020 Sep 9]. Available from: https://open.fda.gov/apis/device/covid19serology/

570. sars-covid-19-detection-test-leaflet.pdf [Internet]. [cited 2020 Apr 21]. Available from: https://v3.globalcube.net/clients/beldico/content/medias/products/microbiology/sars-covid-19-detection-test-leaflet.pdf

571. 210415-status-validatie-sars-cov-2-antigeen-sneltesten_210415_final.pdf [Internet]. [cited 2021 Apr 21]. Available from: https://www.nvmm.nl/media/4120/210415-status-validatie-sars-cov-2-antigeen-sneltesten_210415_final.pdf

572. Peto T, Team UC-19 LFO. COVID-19: Rapid Antigen detection for SARS-CoV-2 by lateral flow assay: a national systematic evaluation for mass-testing. medRxiv. 2021 Jan 26;2021.01.13.21249563.

573. Guglielmi G. Fast coronavirus tests: what they can and can't do. Nature. 2020 Sep 16;585(7826):496–8.

574. Brümmer LE, Katzenschlager S, Gaeddert M, Erdmann C, Schmitz S, Bota M, et al. Accuracy of novel antigen rapid diagnostics for SARS-CoV-2: A living systematic review and meta-analysis. PLoS Med. 2021 Aug;18(8):e1003735.

575. Kohmer N, Toptan T, Pallas C, Karaca O, Pfeiffer A, Westhaus S, et al. The Comparative Clinical Performance of Four SARS-CoV-2 Rapid Antigen Tests and Their Correlation to Infectivity In Vitro. Journal of Clinical Medicine. 2021 Jan;10(2):328.

576. Scheiblauer H, Filomena A, Nitsche A, Puyskens A, Corman VM, Drosten C, et al. Comparative sensitivity evaluation for 122 CE-marked rapid diagnostic tests for SARS-CoV-2 antigen, Germany, September 2020 to April 2021. Eurosurveillance. 2021 Nov 4;26(44):2100441.

577. Uwamino Y, Nagata M, Aoki W, Nakagawa T, Inose R, Yokota H, et al. Accuracy of rapid antigen detection test for nasopharyngeal swab specimens and saliva samples in comparison with RT-PCR and viral culture for SARS-CoV-2 detection. J Infect Chemother. 2021 Jul;27(7):1058–62.

578. Azzi L, Maurino V, Baj A, Dani M, d'Aiuto A, Fasano M, et al. Diagnostic Salivary Tests for SARS-CoV-2. J Dent Res. 2020 Oct 31;0022034520969670.

579. Agulló V, Fernández-González M, Ortiz de la Tabla V, Gonzalo-Jiménez N, García JA, Masiá M, et al. Evaluation of the rapid antigen test Panbio COVID-19 in saliva and nasal swabs in a population-based point-of-care study. J Infect. 2020 Dec 9;

580. Igloi Z, Velzing J, Huisman R, Geurtsvankessel C, Comvalius A, Beek J van, et al. Clinical evaluation of the SD Biosensor saliva antigen rapid test with symptomatic and asymptomatic, non-hospitalized patients. medRxiv. 2021 Apr 21;2021.04.21.21255865.

581. Kritikos A, Caruana G, Brouillet R, Miroz J-P, Samia A-M, Geraldine S, et al. Sensitivity of rapid antigen testing and RT-PCR performed on nasopharyngeal swabs versus saliva samples in COVID-19 hospitalized patients: results of a prospective comparative trial (RESTART). medRxiv. 2021 Apr 15;2021.04.09.21255105.

582. Nagura-Ikeda M, Imai K, Tabata S, Miyoshi K, Murahara N, Mizuno T, et al. Clinical Evaluation of Self-Collected Saliva by Quantitative Reverse Transcription-PCR (RT-qPCR), Direct RT-qPCR, Reverse Transcription-Loop-Mediated Isothermal Amplification, and a Rapid Antigen Test To Diagnose COVID-19. J Clin Microbiol. 2020 Aug 24;58(9).

583. Seitz T, Schindler S, Winkelmeyer P, Zach B, Wenisch C, Zoufaly A, et al. Evaluation of rapid antigen tests based on saliva for the detection of SARS-CoV-2. J Med Virol. 2021 Jul;93(7):4161–2.

584. Favresse J, Gillot C, Oliveira M, Cadrobbi J, Elsen M, Eucher C, et al. Head-to-Head Comparison of Rapid and Automated Antigen Detection Tests for the Diagnosis of SARS-CoV-2 Infection. J Clin Med. 2021 Jan 13;10(2).

585. Lefever S, Indevuyst C, Cuypers L, Dewaele K, Yin N, Cotton F, et al. Comparison of the quantitative DiaSorin Liaison antigen test to RT-PCR for the diagnosis of COVID-19 in symptomatic and asymptomatic outpatients.

586. Li Z, Yi Y, Luo X, Xiong N, Liu Y, Li S, et al. Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis. Journal of Medical Virology

[Internet]. [cited 2020 Apr 21];n/a(n/a). Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.25727

587. Gonzalez JM, Shelton JW, Diaz-Vallejo M, Rodriguez-Castellanos VE, Zuluaga JDH, Chamorro DF, et al. Immunological assays for SARS-CoV-2: an analysis of available commercial tests to measure antigen and antibodies [Internet]. Infectious Diseases (except HIV/AIDS); 2020 Apr [cited 2020 Apr 21]. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.04.10.20061150

588. Mina MJ, Parker R, Larremore DB. Rethinking Covid-19 Test Sensitivity — A Strategy for Containment. New England Journal of Medicine [Internet]. 2020 Sep 30 [cited 2020 Oct 15]; Available from: https://www.nejm.org/doi/10.1056/NEJMp2025631

589. Larremore DB, Wilder B, Lester E, Shehata S, Burke JM, Hay JA, et al. Test sensitivity is secondary to frequency and turnaround time for COVID-19 surveillance. medRxiv. 2020 Sep 8;2020.06.22.20136309.

590. Plebani M, Aita A, Cattelan AM, Bonfante F, Padoan A, Giaquinto C, et al. Frequent testing regimen based on salivary samples for an effective COVID-19 containment strategy. medRxiv. 2020 Oct 14;2020.10.13.20210013.

591. Hellewell J, Russell TW, Team TSI and FS, Consortium TCC-19, Group CC-19 working, Beale R, et al. Estimating the effectiveness of routine asymptomatic PCR testing at different frequencies for the detection of SARS-CoV-2 infections. medRxiv. 2020 Nov 24;2020.11.24.20229948.

592. Holmdahl I, Kahn R, Hay J, Buckee CO, Mina M. Frequent testing and immunity-based staffing will help mitigate outbreaks in nursing home settings. medRxiv. 2020 Nov 23;2020.11.04.20224758.

593. Chang JT, Crawford FW, Kaplan EH. Repeat SARS-CoV-2 Testing Models for Residential College Populations. medRxiv. 2020 Jul 16;2020.07.09.20149351.

594. Chin ET, Lo NC, Huynh BQ, Murrill M, Basu S. Frequency of routine testing for SARS-CoV-2 to reduce transmission among workers. medRxiv. 2020 May 6;

595. Nash B, Badea A, Reddy A, Bosch M, Salcedo N, Gomez AR, et al. The impact of high frequency rapid viral antigen screening on COVID-19 spread and outcomes: a validation and modeling study. medRxiv. 2020 Sep 28;2020.09.01.20184713.

596. Grassly NC, Pons-Salort M, Parker EPK, White PJ, Ferguson NM, Imperial College COVID-19 Response Team. Comparison of molecular testing strategies for COVID-19 control: a mathematical modelling study. Lancet Infect Dis. 2020;20(12):1381–9.

597. Atkeson A, Droste M, Mina MJ, Stock JH. Economic Benefits of COVID-19 Screening Tests. medRxiv. 2020 Nov 1;2020.10.22.20217984.

598. Bootsma MCJ, Kretzschmar ME, Rozhnova G, Heesterbeek J a. P, Kluytmans J, Bonten MJM. Regular universal screening for SARS-CoV-2 infection may not allow reopening of society after controlling a pandemic wave. medRxiv. 2020 Nov 18;2020.11.18.20233122.

599. Bosetti P, Kiem CT, Yazdanpanah Y, Fontanet A, Lina B, Colizza V, et al. Impact of mass testing during an epidemic rebound of SARS-CoV-2: a modelling study using the example of France. Eurosurveillance. 2021 Jan 7;26(1):2001978.

600. Libin P, Willem L, Verstraeten T, Torneri A, Vanderlocht J, Hens N. Assessing the feasibility and effectiveness of household-pooled universal testing to control COVID-19 epidemics. medRxiv. 2020 Oct 6;2020.10.03.20205765.

601. Foladori P, Cutrupi F, Segata N, Manara S, Pinto F, Malpei F, et al. SARS-CoV-2 from faeces to wastewater treatment: What do we know? A review. Sci Total Environ. 2020 Nov 15;743:140444.

602. Kitajima M, Ahmed W, Bibby K, Carducci A, Gerba CP, Hamilton KA, et al. SARS-CoV-2 in wastewater: State of the knowledge and research needs. Sci Total Environ. 2020 Oct 15;739:139076.

603. Liu Y, Gayle AA, Wilder-Smith A, Rocklöv J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. Journal of Travel Medicine. 2020 Feb 13;taaa021.

604. Salje H, Kiem CT, Lefrancq N, Courtejoie N, Bosetti P, Paireau J, et al. Estimating the burden of SARS-CoV-2 in France. Science [Internet]. 2020 May 13 [cited 2020 May 18]; Available from: https://science.sciencemag.org/content/early/2020/05/12/science.abc3517

605. Jarvis CI, Van Zandvoort K, Gimma A, Prem K, CMMID COVID-19 working group, Klepac P, et al. Quantifying the impact of physical distance measures on the transmission of COVID-19 in the UK. BMC Med. 2020 07;18(1):124.

606. Flaxman S, Mishra S, Gandy A, Unwin HJT, Mellan TA, Coupland H, et al. Estimating the effects of non-pharmaceutical interventions on COVID-19 in Europe. Nature. 2020 Jun 8;1–8.

607. Chan KH, Peiris JSM, Lam SY, Poon LLM, Yuen KY, Seto WH. The Effects of Temperature and Relative Humidity on the Viability of the SARS Coronavirus. Adv Virol. 2011;2011:734690.

608. Gardner EG, Kelton D, Poljak Z, Van Kerkhove M, von Dobschuetz S, Greer AL. A case-crossover analysis of the impact of weather on primary cases of Middle East respiratory syndrome. BMC Infectious Diseases. 2019 Feb 4;19(1):113.

609. Lin K, Yee-Tak Fong D, Zhu B, Karlberg J. Environmental factors on the SARS epidemic: air temperature, passage of time and multiplicative effect of hospital infection. Epidemiol Infect. 2006 Apr;134(2):223–30.

610. Demongeot J, Flet-Berliac Y, Seligmann H. Temperature Decreases Spread Parameters of the New Covid-19 Case Dynamics. Biology. 2020 May;9(5):94.

611. Navel V, Chiambaretta F, Dutheil F. Will environmental impacts of social distancing due to the SARS-CoV-2 pandemic decrease allergic disease? J Allergy Clin Immunol. 2020 Apr 26;

612. Xie J, Zhu Y. Association between ambient temperature and COVID-19 infection in 122 cities from China. Science of The Total Environment. 2020 Jul 1;724:138201.

613. Ujiie M, Tsuzuki S, Ohmagari N. Effect of temperature on the infectivity of COVID-19. International Journal of Infectious Diseases. 2020 Jun 1;95:301–3.

614. Yang W, Deng M, Li C, Huang J. Spatio-Temporal Patterns of the 2019-nCoV Epidemic at the County Level in Hubei Province, China. International Journal of Environmental Research and Public Health. 2020 Apr 7;17:2563–73.

615. Majumder P, Ray PP. A systematic review and meta-analysis on correlation of weather with COVID-19. Sci Rep. 2021 May 24;11(1):10746.

616. Paraskevis D, Kostaki EG, Alygizakis N, Thomaidis NS, Cartalis C, Tsiodras S, et al. A review of the impact of weather and climate variables to COVID-19: In the absence of public health measures high temperatures cannot probably mitigate outbreaks. Sci Total Environ. 2021 May 10;768:144578.

617. Meo SA, Abukhalaf AA, Alomar AA, Al-Beeshi IZ, Alhowikan A, Shafi KM, et al. Climate and COVID-19 pandemic: effect of heat and humidity on the incidence and mortality in world's top ten hottest and top ten coldest countries. Eur Rev Med Pharmacol Sci. 2020 Aug;24(15):8232–8.

618. Mehraeen E, Karimi A, Barzegary A, Vahedi F, Afsahi AM, Dadras O, et al. Predictors of mortality in patients with COVID-19-a systematic review. Eur J Integr Med. 2020 Dec;40:101226.

619. Liu Y, Sun W, Li J, Chen L, Wang Y, Zhang L, et al. Clinical features and progression of acute respiratory distress syndrome in coronavirus disease 2019. medRxiv. 2020 Feb 27;2020.02.17.20024166.

620. van Halem K, Bruyndonckx R, van der Hilst J, Cox J, Driesen P, Opsomer M, et al. Risk factors for mortality in hospitalized patients with COVID-19 at the start of the pandemic in Belgium: a retrospective cohort study. BMC Infectious Diseases. 2020 Nov 27;20(1):897.

621. Emami A, Javanmardi F, Pirbonyeh N, Akbari A. Prevalence of Underlying Diseases in Hospitalized Patients with COVID-19: a Systematic Review and Meta-Analysis. Arch Acad Emerg Med. 2020;8(1):e35.

622. Bajgain KT, Badal S, Bajgain BB, Santana MJ. Prevalence of comorbidities among individuals with COVID-19: A rapid review of current literature. Am J Infect Control. 2021 Feb;49(2):238–46.

623. Naeini MB, Sahebi M, Nikbakht F, Jamshidi Z, Ahmadimanesh M, Hashemi M, et al. A meta-meta-analysis: Evaluation of meta-analyses published in the effectiveness of cardiovascular comorbidities on the severity of COVID-19. Obes Med. 2021 Mar;22:100323.

624. Arman A, Tajik M, Nazemipour M, Ahmadinejad Z, Shahrestanaki SK, Hazrati E, et al. Risk factors of developing critical conditions in Iranian patients with COVID-19. Glob Epidemiol. 2021 Nov;3:100046.

625. Chishinga N, Gandhi NR, Onwubiko UN, Telford C, Prieto J, Smith S, et al. Characteristics and Risk Factors for Hospitalization and Mortality among Persons with COVID-19 in Atlanta Metropolitan Area. medRxiv. 2020 Dec 16;

626. Khedr EM, Daef E, Mohamed-Hussein A, Mostafa EF, Zein M, Hassany SM, et al. Impact of comorbidities on COVID-19 outcome. medRxiv. 2020 Nov 30;2020.11.28.20240267.

627. Hwang J-M, Kim J-H, Park J-S, Chang MC, Park D. Neurological diseases as mortality predictive factors for patients with COVID-19: a retrospective cohort study. Neurol Sci. 2020 Sep;41(9):2317–24.

628. Kaeuffer C, Hyaric CL, Fabacher T, Mootien J, Dervieux B, Ruch Y, et al. Clinical characteristics and risk factors associated with severe COVID-19: prospective analysis of 1,045 hospitalised cases in North-Eastern France, March 2020. Eurosurveillance. 2020 Dec 3;25(48):2000895.

629. Nachtigall I, Lenga P, Jóźwiak K, Thürmann P, Meier-Hellmann A, Kuhlen R, et al. Clinical course and factors associated with outcomes among 1904 patients hospitalized with COVID-19 in Germany: an observational study. Clin Microbiol Infect. 2020 Dec;26(12):1663–9.

630. de Souza CD, de Arruda Magalhães AJ, Lima AJ, Nunes DN, de Fátima Machado Soares É, de Castro Silva L, et al. Clinical manifestations and factors associated with mortality from COVID-19 in older adults: Retrospective population-based study with 9807 older Brazilian COVID-19 patients. Geriatr Gerontol Int. 2020 Dec;20(12):1177–81.

631. Biswas M, Rahaman S, Biswas TK, Haque Z, Ibrahim B. Association of Sex, Age, and Comorbidities with Mortality in COVID-19 Patients: A Systematic Review and Meta-Analysis. INT. 2021;64(1):36–47.

632. Mukherjee S, Pahan K. Is COVID-19 Gender-sensitive? J Neuroimmune Pharmacol. 2021 Jan 6;

633. La Vignera S, Cannarella R, Condorelli RA, Torre F, Aversa A, Calogero AE. Sex-Specific SARS-CoV-2 Mortality: Among Hormone-Modulated ACE2 Expression, Risk of Venous Thromboembolism and Hypovitaminosis D. Int J Mol Sci. 2020 Apr 22;21(8).

634. Liu W, Tao Z-W, Lei W, Ming-Li Y, Kui L, Ling Z, et al. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chin Med J. 2020 Feb 28;

635. Gülsen A, Yigitbas BA, Uslu B, Drömann D, Kilinc O. The effect of smoking on COVID-19 symptom severity: Systematic review and meta-analysis. medRxiv. 2020 Aug 17;2020.08.15.20102699.

636. Gasmi A, Peana M, Pivina L, Srinath S, Gasmi Benahmed A, Semenova Y, et al. Interrelations between COVID-19 and other disorders. Clin Immunol. 2020 Dec 14;224:108651.

637. Hussain A, Mahawar K, Xia Z, Yang W, El-Hasani S. Obesity and mortality of COVID-19. Meta-analysis. Obes Res Clin Pract. 2020 Aug;14(4):295–300.

638. Raharja A, Tamara A, Kok LT. Association Between Ethnicity and Severe COVID-19 Disease: a Systematic Review and Meta-analysis. J Racial Ethn Health Disparities. 2020 Nov 12;

639. Sze S, Pan D, Gray LJ, Nevill CR, Martin CA, Nazareth J, et al. Ethnicity and clinical outcomes in COVID-19 A Systematic Review and Meta-analysis. medRxiv. 2020 Sep 8;2020.09.05.20188821.

640. The ABO blood group locus and a chromosome 3 gene cluster associate with SARS-CoV-2 respiratory failure in an Italian-Spanish genome-wide association analysis | medRxiv [Internet]. [cited 2020 Jun 11]. Available from: https://www.medrxiv.org/content/10.1101/2020.05.31.20114991v1

641. Zhao J, Yang Y, Huang H-P, Li D, Gu D-F, Lu X-F, et al. Relationship between the ABO Blood Group and the COVID-19 Susceptibility [Internet]. Epidemiology; 2020 Mar [cited 2020 Mar 22]. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.03.11.20031096

642. Zietz M, Tatonetti NP. Testing the association between blood type and COVID-19 infection, intubation, and death. medRxiv [Internet]. 2020 Apr 11 [cited 2020 Jun 11]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7276013/

643. Delanghe JR, Speeckaert MM, De Buyzere ML. The host's angiotensin-converting enzyme polymorphism may explain epidemiological findings in COVID-19 infections. Clin Chim Acta. 2020 Jun;505:192–3.

644. Team NCPERE. PRIME PubMed | [The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China [Internet]. [cited 2020 Mar 26]. Available from: https://www.unboundmedicine.com/medline/citation/32064853/%5BThe_epidemiological_characteristics_of_an_outbreak_of_2019_novel_coronavirus_diseases__COVID_19__in_China%5D_%20%20

645. Smith C, Odd D, Harwood R, Ward J, Linney M, Clark M, et al. Deaths in Children and Young People in England following SARS-CoV-2 infection during the first pandemic year: a national study using linked mandatory child death reporting data [Internet]. 2021 Jul [cited 2021 Sep 14] p. 2021.07.07.21259779. Available from: https://www.medrxiv.org/content/10.1101/2021.07.07.21259779v1

646. Delahoy MJ. Hospitalizations Associated with COVID-19 Among Children and Adolescents — COVID-NET, 14 States, March 1, 2020–August 14, 2021. MMWR Morb Mortal Wkly Rep [Internet]. 2021 [cited 2021 Sep 14];70. Available from: https://www.cdc.gov/mmwr/volumes/70/wr/mm7036e2.htm

647. Office for National Statistics. Updated estimates of the prevalence of post-acute symptoms among people with coronavirus (COVID-19) in the UK: 26 April 2020 to 1 August 2021 [Internet]. London: ONS; 2021 Sep. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/articles/technicalarticleupdatedestimatesoftheprevalenceofpostacutesymptomsamongpeoplewithcoronaviruscovid19intheuk/26april2020to1august2021#approach-2-prevalence-of-continuous-symptoms-after-infection

648. Molteni E, Sudre CH, Canas LS, Bhopal SS, Hughes RC, Antonelli M, et al. Illness duration and symptom profile in symptomatic UK school-aged children tested for SARS-CoV-2. The Lancet Child & Adolescent Health [Internet]. 2021 Aug 3 [cited 2021 Aug 23];0(0). Available from: https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(21)00198-X/abstract

649. Gudbjartsson DF, Helgason A, Jonsson H, Magnusson OT, Melsted P, Norddahl GL, et al. Spread of SARS-CoV-2 in the Icelandic Population. N Engl J Med. 2020 Apr 14;NEJMoa2006100.

650. Lavezzo E, Franchin E, Ciavarella C, Cuomo-Dannenburg G, Barzon L, Del Vecchio C, et al. Suppression of a SARS-CoV-2 outbreak in the Italian municipality of Vo'. Nature. 2020 Jun 30;1–5.

651. Stringhini S, Wisniak A, Piumatti G, Azman AS, Lauer SA, Baysson H, et al. Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Geneva, Switzerland (SEROCoV-POP): a population-based study. The Lancet. 2020 Aug;396(10247):313–9.

652. Pollán M, Pérez-Gómez B, Pastor-Barriuso R, Oteo J, Hernán MA, Pérez-Olmeda M, et al. Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study. The Lancet [Internet]. 2020 Jul 6 [cited 2020 Jul 31];0(0). Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31483-5/abstract

653. Li X, Xu W, Dozier M, He Y, Kirolos A, Theodoratou E. The role of children in transmission of SARS-CoV-2: A rapid review. J Glob Health [Internet]. [cited 2020 Jul 26];10(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7323934/

654. Davies NG, Klepac P, Liu Y, Prem K, Jit M, Eggo RM. Age-dependent effects in the transmission and control of COVID-19 epidemics. Nature Medicine. 2020 Jun 16;1–7.

655. Mizumoto K, Omori R, Nishiura H. Age specificity of cases and attack rate of novel coronavirus disease (COVID-19). medRxiv. 2020 Mar 13;2020.03.09.20033142.

656. Zhang J, Litvinova M, Liang Y, Wang Y, Wang W, Zhao S, et al. Changes in contact patterns shape the dynamics of the COVID-19 outbreak in China. Science [Internet]. 2020 Apr 29 [cited 2020 May 15]; Available from: https://science.sciencemag.org/content/early/2020/05/04/science.abb8001

657. Roland AM& D. The missing link? Children and transmission of SARS-CoV-2. Don't Forget The Bubbles [Internet]. 2020 May 5 [cited 2020 Jul 31]; Available from: ://dontforgetthebubbles.com//the-missing-link-children-and-transmission-of-sars-cov-2/

658. Viner RM, Mytton OT, Bonell C, Melendez-Torres GJ, Ward J, Hudson L, et al. Susceptibility to SARS-CoV-2 Infection Among Children and Adolescents Compared With Adults: A Systematic Review and Meta-analysis. JAMA Pediatr [Internet]. 2020 Sep 25 [cited 2020 Sep 28]; Available from: https://jamanetwork.com/journals/jamapediatrics/fullarticle/2771181

659. Somekh E, Gleyzer A, Heller E, Lopian M, Kashani-Ligumski L, Czeiger S, et al. The Role of Children in the Dynamics of Intra Family Coronavirus 2019 Spread in Densely Populated Area. The Pediatric Infectious Disease Journal. 2020 Aug;39(8):e202.

660. Mizumoto K, Omori R, Nishiura H. Age specificity of cases and attack rate of novel coronavirus disease (COVID-19) [Internet]. Infectious Diseases (except HIV/AIDS); 2020 Mar [cited 2020 Mar 31]. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.03.09.20033142

661. Lee P-I, Hu Y-L, Chen P-Y, Huang Y-C, Hsueh P-R. Are children less susceptible to COVID-19? Journal of Microbiology, Immunology and Infection [Internet]. 2020 Feb 25 [cited 2020 Mar 11]; Available from: http://www.sciencedirect.com/science/article/pii/S1684118220300396

662. Loenenbach A, Markus I, Lehfeld A-S, Heiden M an der, Haas W, Kiegele M, et al. SARS-CoV-2 variant B.1.1.7 susceptibility and infectiousness of children and adults deduced from investigations of childcare centre outbreaks, Germany, 2021. Eurosurveillance. 2021 May 27;26(21):2100433.

663. Public Health England. Investigation of novel SARS-CoV-2 variant: Variant of Concern 202012/01. Technical Briefing 3 [Internet]. London: Public Health England; 2021 Aug p. 19. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/959360/Variant_of_Concern_VOC_202012_01_Technical_Briefing_3.pdf

664. Callies M, Desombere I, Duysburgh E, Kabouche I, Merckx J. PREVALENCE AND INCIDENCE OF ANTIBODIES AGAINST SARS-COV-2 IN CHILDREN AND SCHOOL STAFF MEASURED BETWEEN DECEMBER 2020 AND JUNE 2021: AN OBSERVATIONAL SERO-PREVALENCE PROSPECTIVE COHORT STUDY [Internet]. Brussels; p. 3. Available from: https://www.sciensano.be/sites/default/files/report_seroprev_sars-cov-2_schools_t2_march2021.pdf

665. Hyde Z. COVID-19, children, and schools: overlooked and at risk. The Medical Journal of Australia. 2020 Aug 12;1.

666. Ludvigsson JF. Children are unlikely to be the main drivers of the COVID-19 pandemic – A systematic review. Acta Paediatrica. 2020;109(8):1525–30.

667. L'Huillier AG, Torriani G, Pigny F, Kaiser L, Eckerle I. Shedding of infectious SARS-CoV-2 in symptomatic neonates, children and adolescents [Internet]. Infectious Diseases (except HIV/AIDS); 2020 May [cited 2020 Jun 5]. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.04.27.20076778

668. Jones TC, Mühlemann B, Veith T, Zuchowski M, Hofmann J, Stein A, et al. An analysis of SARS-CoV-2 viral load by patient age. :19.

669. Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. The Lancet Infectious Diseases [Internet]. 2020 Mar 25 [cited 2020 Mar 26];0(0). Available from: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30198-5/abstract

670. Zhu Y, Bloxham CJ, Hulme KD, Sinclair JE, Tong ZWM, Steele LE, et al. Children are unlikely to have been the primary source of household SARS-CoV-2 infections. medRxiv. 2020 Mar 30;2020.03.26.20044826.

671. Posfay-Barbe KM, Wagner N, Gauthey M, Moussaoui D, Loevy N, Diana A, et al. COVID-19 in Children and the Dynamics of Infection in Families. Pediatrics. 2020 Aug;146(2):e20201576.

672. Merckx J, Labrecque JA, Kaufman JS. Transmission of SARS-CoV-2 by Children. Dtsch Arztebl Int. 2020 21;117(33–34):553–60.

673. Kim J, Choe YJ, Lee J, Park YJ, Park O, Han MS, et al. Role of children in household transmission of COVID-19. Arch Dis Child. 2020 Aug 7;

674. Okarska-Napierała M, Mańdziuk J, Kuchar E. Early Release - SARS-CoV-2 Cluster in Nursery, Poland - Volume 27, Number 1—January 2021 - Emerging Infectious Diseases journal - CDC. [cited 2020 Nov 5]; Available from: https://wwwnc.cdc.gov/eid/article/27/1/20-3849_article

675. Lopez AS, Hill M, Antezano J, Vilven D, Rutner T, Bogdanow L, et al. Transmission Dynamics of COVID-19 Outbreaks Associated with Child Care Facilities — Salt Lake City, Utah, April–July 2020. MMWR Morb Mortal Wkly Rep [Internet]. 2020 Sep 11 [cited 2020 Sep 14];69(37). Available from: http://www.cdc.gov/mmwr/volumes/69/wr/mm6937e3.htm?s_cid=mm6937e3_w

676. Gilliam WS, Malik AA, Shafiq M, Klotz M, Reyes C, Humphries JE, et al. COVID-19 Transmission in US Child Care Programs. Pediatrics [Internet]. 2020 Oct 1 [cited 2020 Nov 5]; Available from: https://pediatrics.aappublications.org/content/early/2020/10/16/peds.2020-031971

677. Heavey L, Casey G, Kelly C, Kelly D, McDarby G. No evidence of secondary transmission of COVID-19 from children attending school in Ireland, 2020. Eurosurveillance. 2020 May 28;25(21):2000903.

678. Fontanet A, Tondeur L, Madec Y, Grant R, Besombes C, Jolly N, et al. Cluster of COVID-19 in northern France: A retrospective closed cohort study. medRxiv. 2020 Apr 23;2020.04.18.20071134.

679. Fontanet A, Grant R, Tondeur L, Madec Y, Grzelak L, Cailleau I, et al. SARS-CoV-2 infection in primary schools in northern France: A retrospective cohort study in an area of high transmission. medRxiv. 2020 Jun 29;2020.06.25.20140178.

680. Macartney K, Quinn HE, Pillsbury AJ, Koirala A, Deng L, Winkler N, et al. Transmission of SARS-CoV-2 in Australian educational settings: a prospective cohort study. The Lancet Child & Adolescent Health [Internet]. 2020 Aug 3 [cited 2020 Aug 17]; Available from: http://www.sciencedirect.com/science/article/pii/S2352464220302510

681. Public Health Agency of Sweden. Covid-19 in schoolchildren. A comparison between Finland and Sweden [Internet]. Report No.: 20108–1. Available from: https://www.folkhalsomyndigheten.se/publicerat-material/publikationsarkiv/c/covid-19-in-schoolchildren/

682. Ismail SA, Saliba V, Bernal JL, Ramsay ME, Ladhani SN. SARS-CoV-2 infection and transmission in educational settings: a prospective, cross-sectional analysis of infection clusters and outbreaks in England. The Lancet Infectious Diseases [Internet]. 2020 Dec 8 [cited 2020 Dec 9];0(0). Available from: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30882-3/abstract

683. Kirsten C, Unrath M, Lück C, Dalpke AH, Berner R, Armann J. SARS-CoV-2 seroprevalence in students and teachers: a longitudinal study from May to October 2020 in German secondary schools. BMJ Open. 2021 Jun 10;11(6):e049876.

684. Ladhani SN, Baawuah F, Beckmann J, Okike IO, Ahmad S, Garstang J, et al. SARS-CoV-2 infection and transmission in primary schools in England in June-December, 2020 (sKIDs): an active, prospective surveillance study. Lancet Child Adolesc Health. 2021 Jun;5(6):417–27.

685. Ulyte A, Radtke T, Abela IA, Haile SR, Berger C, Huber M, et al. Clustering and longitudinal change in SARS-CoV-2 seroprevalence in school children in the canton of Zurich, Switzerland: prospective cohort study of 55 schools. BMJ. 2021 Mar 17;372:n616.

686. Gandini S, Rainisio M, Iannuzzo ML, Bellerba F, Cecconi F, Scorrano L. A cross-sectional and prospective cohort study of the role of schools in the SARS-CoV-2 second wave in Italy. Lancet Reg Health Eur. 2021 Jun;5:100092.

687. Harris D, Ziedan E, Hassig S. The Effects of School Reopenings on COVID-19 Hospitalizations [Internet]. National Centre on Research on Education Access and Choice. Tulane University.; 2021

Jan [cited 2021 Jun 24]. Available from: https://www.reachcentered.org/publications/the-effects-of-school-reopenings-on-covid-19-hospitalizations

688. Goldhaber D, Imberman S, Strunk K, Hopkins B, Brown N, Harbatkin E, et al. To What Extent Does In-Person Schooling Contribute to the Spread of COVID-19? Evidence from Michigan and Washington [Internet]. Cambridge, MA: National Bureau of Economic Research; 2021 Feb [cited 2021 Jun 24] p. w28455. Report No.: w28455. Available from: http://www.nber.org/papers/w28455.pdf

689. Mensah AA, Sinnathamby M, Zaidi A, Coughlan L, Simmons R, Ismail SA, et al. SARS-CoV-2 infections in children following the full re-opening of schools and the impact of national lockdown: Prospective, national observational cohort surveillance, July-December 2020, England. Journal of Infection [Internet]. 2021 Feb 25 [cited 2021 Mar 8]; Available from: https://www.sciencedirect.com/science/article/pii/S0163445321000931

690. Jiang L, Tang K, Levin M, Irfan O, Morris SK, Wilson K, et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. Lancet Infect Dis. 2020 Aug 17;

691. Belot A, Antona D, Renolleau S, Javouhey E, Hentgen V, Angoulvant F, et al. SARS-CoV-2-related paediatric inflammatory multisystem syndrome, an epidemiological study, France, 1 March to 17 May 2020. Eurosurveillance. 2020 Jun 4;25(22):2001010.

692. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. The Lancet. 2020 May 23;395(10237):1607–8.

693. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2. JAMA. 2020 Jun 8;

694. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. The Lancet [Internet]. 2020 May 13 [cited 2020 May 18];0(0). Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31103-X/abstract

695. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. N Engl J Med. 2020 23;383(4):334–46.

696. Davies P, Evans C, Kanthimathinathan HK, Lillie J, Brierley J, Waters G, et al. Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: a multicentre observational study. The Lancet Child & Adolescent Health [Internet]. 2020 Jul 9 [cited 2020 Jul 31];0(0). Available from: https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(20)30215-7/abstract

697. Qiao J. What are the risks of COVID-19 infection in pregnant women? The Lancet. 2020 Mar 7;395(10226):760–2.

698. Chen S, Liao E, Shao Y. Clinical analysis of pregnant women with 2019 novel coronavirus pneumonia. Journal of Medical Virology [Internet]. [cited 2020 Mar 29];n/a(n/a). Available from: http://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.25789

699. Schwartz DA. An Analysis of 38 Pregnant Women with COVID-19, Their Newborn Infants, and Maternal-Fetal Transmission of SARS-CoV-2: Maternal Coronavirus Infections and Pregnancy Outcomes. Arch Pathol Lab Med. 2020 Mar 17;

700. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. The Lancet. 2020 Mar 7;395(10226):809–15.

701. Rasmussen SA, Smulian JC, Lednicky JA, Wen TS, Jamieson DJ. Coronavirus Disease 2019 (COVID-19) and Pregnancy: What obstetricians need to know. American Journal of Obstetrics and Gynecology. 2020 Feb;S0002937820301976.

702. Mullins E, Evans D, Viner RM, O'Brien P, Morris E. Coronavirus in pregnancy and delivery: rapid review. Ultrasound in Obstetrics & Gynecology [Internet]. [cited 2020 Mar 17];n/a(n/a). Available from: https://obgyn.onlinelibrary.wiley.com/doi/abs/10.1002/uog.22014

703. Parazzini F, Bortolus R, Mauri PA, Favilli A, Gerli S, Ferrazzi E. Delivery in pregnant women infected with SARS-CoV-2: A fast review. International Journal of Gynecology & Obstetrics [Internet]. [cited 2020 Apr 18];n/a(n/a). Available from: https://obgyn.onlinelibrary.wiley.com/doi/abs/10.1002/ijgo.13166

704. Knight M, Bunch K, Vousden N, Morris E, Simpson N, Gale C, et al. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. BMJ [Internet]. 2020 Jun 8 [cited 2020 Sep 6];369. Available from: https://www.bmj.com/content/369/bmj.m2107

705. Breslin N, Baptiste C, Gyamfi-Bannerman C, Miller R, Martinez R, Bernstein K, et al. Coronavirus disease 2019 infection among asymptomatic and symptomatic pregnant women: two weeks of confirmed presentations to an affiliated pair of New York City hospitals. Am J Obstet Gynecol MFM. 2020 May;2(2):100118.

706. Collin J, Byström E, Carnahan A, Ahrne M. Pregnant and postpartum women with SARS-CoV-2 infection in intensive care in Sweden. Acta Obstet Gynecol Scand [Internet]. 2020 May 9 [cited 2020 Sep 6]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7273089/

707. Ellington S, Strid P, Tong VT, Woodworth K, Galang RR, Zambrano LD, et al. Characteristics of Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status — United States, January 22–June 7, 2020. MMWR Morb Mortal Wkly Rep. 2020 Jun 26;69(25):769–75.

708. Zambrano LD, Ellington S, Strid P, Galang RR, Oduyebo T, Tong VT, et al. Update: Characteristics of Symptomatic Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status — United States, January 22–October 3, 2020. MMWR Morb Mortal Wkly Rep. 2020 Nov 6;69(44):1641–7.

709. Adhikari EH, Moreno W, Zofkie AC, MacDonald L, McIntire DD, Collins RRJ, et al. Pregnancy Outcomes Among Women With and Without Severe Acute Respiratory Syndrome Coronavirus 2 Infection. JAMA Network Open. 2020 Nov 19;3(11):e2029256–e2029256.

710. Jering KS, Claggett BL, Cunningham JW, Rosenthal N, Vardeny O, Greene MF, et al. Clinical Characteristics and Outcomes of Hospitalized Women Giving Birth With and Without COVID-19. JAMA Intern Med [Internet]. 2021 Jan 15 [cited 2021 Feb 2]; Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2775396

711. Villalaín C, Herraiz I, Luczkowiak J, Pérez-Rivilla A, Folgueira MD, Mejía I, et al. Seroprevalence analysis of SARS-CoV-2 in pregnant women along the first pandemic outbreak and perinatal outcome. PLoS One. 2020;15(11):e0243029.

712. Vivanti AJ, Vauloup-Fellous C, Prevot S, Zupan V, Suffee C, Do Cao J, et al. Transplacental transmission of SARS-CoV-2 infection. Nature Communications. 2020 Jul 14;11(1):3572.

713. Walker KF, O'Donoghue K, Grace N, Dorling J, Comeau JL, Li W, et al. Maternal transmission of SARS-COV-2 to the neonate, and possible routes for such transmission: A systematic review and critical analysis. BJOG: An International Journal of Obstetrics & Gynaecology [Internet]. [cited 2020 Jun 13];n/a(n/a). Available from: http://obgyn.onlinelibrary.wiley.com/doi/abs/10.1111/1471-0528.16362

714. Prabhu M, Cagino K, Matthews KC, Friedlander RL, Glynn SM, Kubiak JM, et al. Pregnancy and postpartum outcomes in a universally tested population for SARS-CoV-2 in New York City: a prospective cohort study. BJOG. 2020 Jul 7;

715. RCOG. Coronavirus (COVID-19) infection and pregnancy [Internet]. Royal College of Obstetricians & Gynaecologists. [cited 2020 Sep 6]. Available from: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/coronavirus-pregnancy/

716. Pique-Regi R, Romero R, Tarca AL, Luca F, Xu Y, Alazizi A, et al. Does the human placenta express the canonical cell entry mediators for SARS-CoV-2? Parker SC, Bronner ME, editors. eLife. 2020 Jul 14;9:e58716.

717. Edlow AG, Li JZ, Collier AY, Atyeo C, James KE, Boatin AA, et al. Assessment of Maternal and Neonatal SARS-CoV-2 Viral Load, Transplacental Antibody Transfer, and Placental Pathology in Pregnancies During the COVID-19 Pandemic. JAMA Network Open. 2020 Dec 22;3(12):e2030455–e2030455.

718. Huntley BJF, Huntley ES, Di Mascio D, Chen T, Berghella V, Chauhan SP. Rates of Maternal and Perinatal Mortality and Vertical Transmission in Pregnancies Complicated by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Co-V-2) Infection: A Systematic Review. Obstetrics & Gynecology [Internet]. 2020 Jun 11 [cited 2020 Jun 13];Publish Ahead of Print. Available from: http://journals.lww.com/greenjournal/Abstract/9000/Rates_of_Maternal_and_Perinatal_Mortality_and.97336.aspx

719. Shanes ED, Mithal LB, Otero S, Azad HA, Miller ES, Goldstein JA. Placental Pathology in COVID-19. Am J Clin Pathol. 2020 08;154(1):23–32.

720. World Health Organization. Breastfeeding and COVID-19 - Scientific Brief [Internet]. 2020 [cited 2020 Sep 6]. Available from: https://www.who.int/news-room/commentaries/detail/breastfeeding-and-covid-19

721. Shalhoub S, AlZahrani A, Simhairi R, Mushtaq A. Successful recovery of MERS CoV pneumonia in a patient with acquired immunodeficiency syndrome: A case report. Journal of Clinical Virology. 2015 Jan 1;62:69–71.

722. Wong AT, Tsang OT, Wong KH, Wong MY, Lim WL, Zheng BJ, et al. Coronavirus infection in an AIDS patient. AIDS [Internet]. 2004;18(5). Available from: https://journals.lww.com/aidsonline/Fulltext/2004/03260/Coronavirus_infection_in_an_AIDS_patient.21.aspx

723. Guo W, Ming F, Dong Y, Zhang Q, Zhang X, Mo P, et al. A Survey for COVID-19 Among HIV/AIDS Patients in Two Districts of Wuhan, China. The Lancet. 2020;

724. Blanco JL, Ambrosioni J, Garcia F, Martínez E, Soriano A, Mallolas J, et al. COVID-19 in patients with HIV: clinical case series. Lancet HIV. 2020 Apr 15;

725. Aydin OA, Karaosmanoglu HK, Yasar KK. HIV/SARS-CoV-2 co-infected patients in Istanbul, Turkey. Journal of Medical Virology [Internet]. [cited 2020 May 7];n/a(n/a). Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.25955

726. Härter G, Spinner CD, Roider J, Bickel M, Krznaric I, Grunwald S, et al. COVID-19 in people living with human immunodeficiency virus: A case series of 33 patients. :7.

727. Zhu F, Cao Y, Xu S, Zhou M. Co-infection of SARS-CoV-2 and HIV in a patient in Wuhan city, China. Journal of Medical Virology. 2020;92(6):529–30.

728. Byrd KM, Beckwith CG, Garland JM, Johnson JE, Aung S, Cu-Uvin S, et al. SARS-CoV-2 and HIV coinfection: clinical experience from Rhode Island, United States. J Int AIDS Soc. 2020;23(7):e25573.

729. Karmen-Tuohy S, Carlucci PM, Zervou FN, Zacharioudakis IM, Rebick G, Klein E, et al. Outcomes Among HIV-Positive Patients Hospitalized With COVID-19. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2020 Sep 1;85(1):6–10.

730. Stoeckle K, Johnston CD, Jannat-Khah DP, Williams SC, Ellman TM, Vogler MA, et al. COVID-19 in Hospitalized Adults With HIV. Open Forum Infect Dis [Internet]. 2020 Aug 1 [cited 2020 Sep 4];7(8). Available from: https://academic.oup.com/ofid/article/7/8/ofaa327/5879769

731. Del Amo J, Polo R, Moreno S, Díaz A, Martínez E, Arribas JR, et al. Incidence and Severity of COVID-19 in HIV-Positive Persons Receiving Antiretroviral Therapy: A Cohort Study. Ann Intern Med. 2020 26;

732. COVID-19 Outcomes Among Persons Living With or Without Diagnosed HIV Infection in New York State [Internet]. Alliance for Pandemic Preparedness. [cited 2021 Feb 6]. Available from: https://depts.washington.edu/pandemicalliance/2021/02/04/covid-19-outcomes-among-persons-living-with-or-without-diagnosed-hiv-infection-in-new-york-state/

733. Mellor M, Bast A, Jones N, Roberts N, Ordonez-Mena J, Reith A, et al. Risk of adverse COVID-19 outcomes for people living with HIV: a rapid review and meta-analysis. medRxiv. 2020 Sep 23;2020.09.22.20199661.

734. Western Cape Department of Health with National Institute for Communicable Diseases SA, Davies M-A. HIV and risk of COVID-19 death: a population cohort study from the Western Cape Province, South Africa. medRxiv. 2020 Jul 3;2020.07.02.20145185.

735. Hadi YB, Naqvi SFZ, Kupec JT, Sarwari AR. Characteristics and outcomes of COVID-19 in patients with HIV: a multi-center research network study. AIDS. 2020 Aug 10;

736. Pinto RM, Park S. COVID-19 Pandemic Disrupts HIV Continuum of Care and Prevention: Implications for Research and Practice Concerning Community-Based Organizations and Frontline Providers. AIDS Behav. 2020 Apr 28;

737. Jiang H, Zhou Y, Tang W. Maintaining HIV care during the COVID-19 pandemic. The Lancet HIV. 2020 May;7(5):e308–9.

738. Salunke AA, Nandy K, Pathak SK, Shah J, Kamani M, Kottakota V, et al. Impact of COVID -19 in cancer patients on severity of disease and fatal outcomes: A systematic review and meta-analysis. Diabetes Metab Syndr. 2020 Jul 28;14(5):1431–7.

739. ElGohary GM, Hashmi S, Styczynski J, Kharfan-Dabaja MA, Alblooshi RM, de la Cámara R, et al. The risk and prognosis of COVID-19 infection in cancer patients: A systematic review and meta-analysis. Hematol Oncol Stem Cell Ther. 2020 Jul 30;

740. Tian Y, Qiu X, Wang C, Zhao J, Jiang X, Niu W, et al. Cancer associates with risk and severe events of COVID-19: A systematic review and meta-analysis. Int J Cancer. 2020 Jul 19;

741. Ofori-Asenso R, Ogundipe O, Agyeman AA, Chin KL, Mazidi M, Ademi Z, et al. Cancer is associated with severe disease in COVID-19 patients: a systematic review and meta-analysis. Ecancermedicalscience. 2020;14:1047.

742. Robilotti EV, Babady NE, Mead PA, Rolling T, Perez-Johnston R, Bernardes M, et al. Determinants of COVID-19 disease severity in patients with cancer. Nat Med. 2020;26(8):1218–23.

743. Zhang H, Wang L, Chen Y, Wu Q, Chen G, Shen X, et al. Outcomes of novel coronavirus disease 2019 (COVID-19) infection in 107 patients with cancer from Wuhan, China. Cancer. 2020 01;126(17):4023–31.

744. Yang K, Sheng Y, Huang C, Jin Y, Xiong N, Jiang K, et al. Clinical characteristics, outcomes, and risk factors for mortality in patients with cancer and COVID-19 in Hubei, China: a multicentre, retrospective, cohort study. Lancet Oncol. 2020;21(7):904–13.

745. Lee LY, Cazier J-B, Angelis V, Arnold R, Bisht V, Campton NA, et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. Lancet. 2020 20;395(10241):1919–26.

746. Kuderer NM, Choueiri TK, Shah DP, Shyr Y, Rubinstein SM, Rivera DR, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. Lancet. 2020 20;395(10241):1907–18.

747. Dai M, Liu D, Liu M, Zhou F, Li G, Chen Z, et al. Patients with Cancer Appear More Vulnerable to SARS-CoV-2: A Multicenter Study during the COVID-19 Outbreak. Cancer Discov. 2020;10(6):783–91.

748. Mehta V, Goel S, Kabarriti R, Cole D, Goldfinger M, Acuna-Villaorduna A, et al. Case Fatality Rate of Cancer Patients with COVID-19 in a New York Hospital System. Cancer Discov. 2020;10(7):935–41.

749. Azambuja E de, Brandão M, Wildiers H, Laenen A, Aspeslagh S, Fontaine C, et al. Impact of solid cancer on in-hospital mortality overall and among different subgroups of patients with COVID-19: a nationwide, population-based analysis. ESMO Open. 2020 Sep 1;5(5):e000947.

750. Passamonti F, Cattaneo C, Arcaini L, Bruna R, Cavo M, Merli F, et al. Clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: a retrospective, multicentre, cohort study. Lancet Haematol. 2020 Aug 13;

751. Yigenoglu TN, Ata N, Altuntas F, Basci S, Dal MS, Korkmaz S, et al. The outcome of COVID-19 in patients with hematological malignancy. J Med Virol. 2020 Aug 10;

752. Jee J, Foote MB, Lumish M, Stonestrom AJ, Wills B, Narendra V, et al. Chemotherapy and COVID-19 Outcomes in Patients With Cancer. J Clin Oncol. 2020 Aug 14;JCO2001307.

753. Kabarriti R, Brodin NP, Maron MI, Tomé WA, Halmos B, Guha C, et al. Extent of Prior Lung Irradiation and Mortality in COVID-19 Patients With a Cancer History. Adv Radiat Oncol. 2020 Aug;5(4):707–10.

754. Kantar A, Mazza A, Bonanomi E, Odoni M, Seminara M, Verde ID, et al. COVID-19 and children with Down syndrome: is there any real reason to worry? Two case reports with severe course. BMC Pediatr. 2020 Dec 18;20(1):561.

755. Vita S, Di Bari V, Corpolongo A, Goletti D, Espinosa J, Petracca S, et al. Down Syndrome patients with COVID-19 pneumonia: A high-risk category for unfavourable outcome. Int J Infect Dis. 2020 Nov 30;103:607–10.

756. Emami A, Javanmardi F, Akbari A, Asadi-Pooya AA. COVID-19 in patients with Down syndrome. Neurol Sci. 2021 Feb 1;

757. Hüls A, Costa ACS, Dierssen M, Baksh RA, Bargagna S, Baumer NT, et al. An international survey on the impact of COVID-19 in individuals with Down syndrome. medRxiv. 2020 Nov 5;2020.11.03.20225359.

758. Altable M, de la Serna JM. Down's syndrome and COVID-19: risk or protection factor against infection? A molecular and genetic approach. Neurol Sci. 2021 Feb;42(2):407–13.

759. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin–Angiotensin–Aldosterone System Blockers and the Risk of Covid-19. New England Journal of Medicine. 2020 Jun 18;382(25):2431–40.

760. Reynolds HR, Adhikari S, Pulgarin C, Troxel AB, Iturrate E, Johnson SB, et al. Renin–Angiotensin–Aldosterone System Inhibitors and Risk of Covid-19. New England Journal of Medicine. 2020 Jun 18;382(25):2441–8.

761. Cohen JB, Hanff TC, William P, Sweitzer N, Rosado-Santander NR, Medina C, et al. Continuation versus discontinuation of renin–angiotensin system inhibitors in patients admitted to hospital with COVID-19: a prospective, randomised, open-label trial. The Lancet Respiratory Medicine [Internet]. 2021 Jan 7 [cited 2021 Feb 4];0(0). Available from: https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30558-0/abstract

762. Lund LC, Kristensen KB, Reilev M, Christensen S, Thomsen RW, Christiansen CF, et al. Adverse outcomes and mortality in users of non-steroidal anti-inflammatory drugs who tested positive for SARS-CoV-2: A Danish nationwide cohort study. PLOS Medicine. 2020 Sep 8;17(9):e1003308.