

# Independent High Risk AGP Panel systematic review: background paper

## Introduction

Aerosol Generating Procedures (AGPs) are commonly presumed to be any medical or patient care procedure that results in the production of airborne particles (aerosols). However, the World Health Organization (WHO) recommends the application of enhanced precautions for 'high-risk AGPs' which are defined as medical procedures that 'have been reported to be aerosol-generating and consistently associated with an increased risk of pathogen transmission' [WHO, 2014].

The purpose of this evidence review was to inform recommendations for medical procedures which do not meet the WHO definition for high risk AGP to date, however are subject to professional society and organisational concerns, about their potential for generating infectious aerosols of Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2). These are procedures which may induce coughing, heavy breathing or sneezing in the patient undergoing the procedure. The procedures included in the review were: nasogastric tube insertion, cardiopulmonary exercise and lung function tests, spirometry, swallowing assessment, nas(o)endoscopy, nasal cautery and suction in the context of airway clearance (not associated with intubation or mechanical ventilation). The review sought to evaluate evidence that these procedures generate infectious aerosols and are associated with a risk of transmission of respiratory infection, inclusive of SARS-CoV-2.

## Background

Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) is an enveloped RNA virus with a characteristic crown-like surface when viewed under the electron microscope, which causes the disease COVID-19. Most coronaviruses infect animals (bats, birds and mammals), which act as intermediate hosts and are potential reservoirs for human infection. Four of the seven coronaviruses known to infect humans cause mild to moderate disease such as common colds, lower respiratory tract infections, croup and bronchiolitis. The other three have emerged in the last 20 years and have the propensity to cause more severe disease: SARS-CoV-1 (Severe Acute Respiratory Syndrome - SARS) in 2002, MERS-CoV (Middle East Respiratory Syndrome - MERS) in 2012, and SARS-CoV-2, identified in late 2019 [ECDC, 2020a].

The incubation period of COVID-19, which is the time between exposure to the virus and symptom onset, is on average 5-6 days, but can be as long as 14 days with the majority of symptomatic cases (97.5%) presenting by day 12 [Yu et al., 2020; Lauer et al., 2020; Backer et al., 2020].

Mild COVID-19 disease may be associated with a range of general symptoms (e.g., headache, fever, fatigue) and symptoms affecting the upper respiratory tract (e.g., cough, nasal obstruction, rhinorrhoea, loss of smell/taste, sore throat) and sometimes the gastrointestinal tract [Lechien et al., 2020]. More severe cases admitted to hospital also present with shortness of breath and/or confusion [Docherty et al., 2020]. SARS-CoV-2 can cause diffuse alveolar damage similar to that associated with other respiratory viruses, such as MERS-CoV and influenza virus. Some patients might develop one of several longer-term syndromes and these are being characterised by a number of groups [NIHR, 2020].

## Detection of virus

Viral RNA has been detected in respiratory tract specimens 1-2 days before the onset of symptoms and can persist for up to eight days in mild cases, longer in more severe cases and the immunocompromised [Liu et al., 2020]. Shedding of viral RNA is highest at the time of symptom onset, although shedding can occur for several days prior to the onset of symptoms [He et al., 2020]. Viral load can be a marker of disease severity and prognosis, with viral loads in severe cases up to 60 times higher than in mild cases [Liu et al., 2020]. Important lessons have been learnt in the viral dynamics of SARS-Cov-2; the peak viral load is at the time of symptom onset, which is similar to influenza but unlike SARS-CoV-1, which peaks later at around 10 days after symptom onset [Chang et al., 2020]. This has been demonstrated by the detection of SARS-CoV-2 in the upper respiratory tract e.g., nose and throat in the first week of illness [Wolfel et al., 2020]. The high viral load close to symptom onset suggests that SARS-CoV-2 is transmissible at an early stage of infection [Lavezzo et al., 2020] and studies have confirmed onward transmission in the pre-symptomatic period.

Virus detection by reverse transcription – polymerase chain reaction (RT-PCR) is widely used to infer the infectivity of an individual, however, RT-PCR does not distinguish between infectious (viable) and non-infectious (non-viable) virus. Viral culture is used to determine viable infectious virus and studies that cultivate virus to determine infectiousness confirm viable infectious virus is detected from day 8-10 from onset of symptoms, with <6% beyond day 10 of onset. [Singanayagam et al., 2020] Viral sub genomic RNA (intermediates of viral replication) can be used as a marker of SARS-CoV-2 infectiousness and has been found to be positive up to 8 days after symptoms onset [Perera et al., 2020].

## Implications of SARS-CoV-2 tests in the interpretation of evidence

Testing for acute infection and in some of the studies cited in this review, relies on molecular techniques aimed at detecting a variety of different genetic targets. The majority of these are based on RT-PCR, although other techniques, particularly for asymptomatic testing, are now being used in addition to RT-PCR across the UK. These include loop-mediated isothermal amplification (LAMP) which is not based on the extraction and amplification of RNA and can be used as a rapid screening test to identify very strong positive samples with high viral loads, although sensitivity drops markedly where viral load is lower. Lateral flow tests (LFT) detect SARS-CoV-2 nucleocapsid proteins without the need for lab processing, but because they do not involve an amplification step, they are likely to miss mild or early-stage cases with lower viral loads [NHSE, 2020].

There are a number of limitations that exist for testing methods:

1. The overall sensitivity and specificity of the test is highly dependent on sample type and quality. With current assays, lower respiratory samples have a higher rate of positivity than upper respiratory samples from known COVID-19 patients [Wang et al., 2020; Yang et al., 2020].
2. Whilst the diagnostic performance of these assays is generally quite high (with sensitivity and specificity of > 90%), the best performance of all the assays to date requires an extraction step to remove contaminating nucleic acid from the sample and purify the viral RNA, particularly in those samples with lower viral load. Without this step, most assays quote a sensitivity and specificity of around 80%, which has the potential to generate significant numbers of false positive and negative results. This can be increased by the application of testing criteria, which raises the possibility that the person being tested has the infection before the test is done (i.e. increasing the pre-test probability of a correct result) [Watson et al., 2020].
3. Similarly, there are some concerns around false positives at the very extreme end of detection. The cycle threshold (Ct) refers to the number of amplification cycles required before the amount of viral RNA exceeds the background level. A low Ct value e.g. less than 30 is considered a strong positive reaction indicative of abundant target nucleic acid in the cycle. High Ct value e.g. greater than 37, reflect a weak reaction which may or may not indicate infection. Setting evidence-based and consistent clinical cut-offs for each assay is therefore essential to ensuring the result is interpreted correctly (i.e. increasing the post-test probability of a positive result) [Vogels et al., 2020].
4. The overall positive and negative predictive values of the test (PPV, NPV; the chance that a positive is a true positive or a negative is a true negative, respectively) is dependent on the prevalence of the infection within the population at the time. This is difficult to calculate in real time given the assumed large numbers of the population who may have asymptomatic infection and will not present for a test.

5. Although the assays are able to detect very small levels of virus present, none are able to ascertain whether the virus is viable or not, and so the test itself cannot predict whether a patient is infectious or not. This is particularly relevant towards the end of the clinical episode in the healthcare setting as it has implications for removing isolation and other infection prevention and control precautions.
6. There is currently no test capable of detecting when a person is incubating the virus following exposure to an infectious case and before the establishment of the infection process. This means that prolonged periods of self-isolation are required for those exposed to infection.

## Asymptomatic infections

One living systematic review has so far included 79 empirical observational studies which followed up patients who were asymptomatic when diagnosed by positive SARS-CoV-2 test (a total of 6,832 people). This evidence synthesis estimated that 20% (95% CI 17-25) remained asymptomatic throughout the follow-up period [Buitrago-Garcia et al., 2020]. Interpretation of these type of studies is affected by variation (or absence) of case definitions and whether patients who develop mild symptoms are classified as asymptomatic [Buitrago-Garcia et al., 2020].

Although presymptomatic transmission occurs, the secondary attack rate (SAR) (probability of infection among susceptible persons following known contact with an infectious person) was lower in contacts of people with asymptomatic infection than those with symptomatic infection. However, with a relative risk of 0.35 (95% CI 0.10 - 1.27) more studies are required to quantify the risk more precisely [Buitrago-Garcia et al., 2020].

A systematic review of empirical data from 43 studies estimated the SAR of SARS-CoV-2 in household settings as 18.1% (95% CI: 15.7%, 20.6%) [Koh et al., 2020]. Although there was considerable heterogeneity between studies, the SAR is considerably lower than viruses known to be transmitted via aerosols such as measles, where the SAR is in the region of 90% [WHO, 2012; CDC, 1996]. However, more prospective studies designed to minimise selection and measurement bias are required to develop more precise estimates. Understanding the secondary attack rate helps inform policy [Cevik et al., 2020].

## Routes of transmission for SARS-CoV-2

SARS-CoV-2 transmission appears to mainly occur via droplets and close contact with infected symptomatic cases [WHO, 2020a]. Airborne transmission, due to dissemination of droplet nuclei (aerosols) which remain infectious when suspended in air over prolonged periods, can occur during some medical procedures involving the respiratory tract, which generate aerosols. The scientific community has been considering evidence that aerosols contribute to the spread of SARS-CoV-2 in other situations such as prolonged, close contact in indoor settings with poor ventilation.

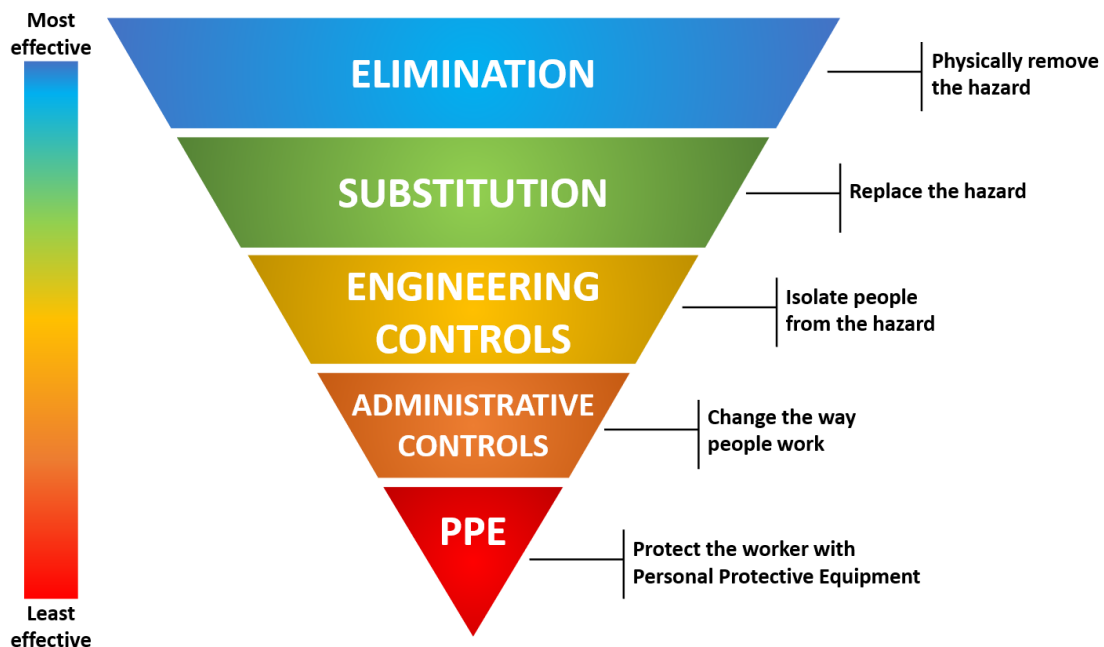
# The Hierarchy of Controls

Managing the risk of transmission, both to staff and other patients, requires the application of a range of controls for eliminating the risk to using personal protective equipment (PPE). Health and safety interventions are based on the Hierarchy of Controls [CDC, 2015], which recommends using strategies that reduce the risk of exposure to the virus rather than only relying on the use of PPE, see figure 1. Such strategies include eliminating the hazard by avoiding admission/treatment of people with active infection, using testing to segregate patients with the infection, engineering controls such as physical barriers, and administrative controls such as procedures to facilitate physical distancing [Mahtani et al., 2020; Fong et al., 2020].

However, given physical proximity is required to deliver many elements of care, the use of PPE is also a required control measure within the healthcare environment. The UK-recommended infection control precautions applied to the routine care of patients with COVID-19 are droplet and contact precautions. Droplet precautions require fluid resistant (type IIR) surgical masks (FRSMs) to be worn for close contact with the patient, eye protection and contact precautions, and the use of hand hygiene and/or gloves for contact with the immediate patient environment.

**Figure 1.** A diagrammatic representation of a hierarchy of controls which has traditionally been used as a means of determining how to implement feasible and effective control solutions related to occupational hazards.

Note: Adapted from Hierarchy of Controls (CDC, 2015)



## Respirators & surgical masks in the context of the COVID-19 pandemic

This review has not been tasked to clarify whether FRSMs offer sufficient protection to Healthcare Workers when considering SARS-CoV-2. This would merit a separate review and only a few papers are mentioned here as part of a narrative. However, a recent WHO evaluation of systematic reviews comparing the efficacy of FRSM with Filtering Face Piece (FFP) respirators used during general care found no statistically significant difference in outcomes for healthcare workers in the acquisition of clinical respiratory illness (WHO 2020b).

In the UK, FFP respirators are recommended for use when performing high risk AGPs on patients with acute respiratory infections of concern. Although these respiratory infections are generally transmitted by droplets, aerosols generated during these AGPs have been consistently associated with an increased risk of infection. In the UK, FFP3 respirators (N99 equivalent) are recommended by the Health and Safety Executive (HSE) for use in healthcare settings as they are considered to provide the highest level of protection with an assigned protection factor (APF) of 20. This is equivalent to reducing the wearers exposure by a factor of 20. An FFP2 respirator, which has an APF of 10, is equivalent to a N95, which is widely recommended in other countries. The EU Standard 149 determines the specifications of FFP respirators used in the UK. Previously, the N95 could not be used in the UK as it had not been tested to the European standards and was not CE marked. It is widely accepted by industry that the N95 is comparable to an FFP2. HSE recommends the use of an FFP3 for use against viruses. Whilst FFP3 is the usual recommended UK control measure, it may not be reasonably practicable to use these if global supplies of FFP3 masks are low during a pandemic. In this scenario, an FFP2 could be used as an alternative, as this is consistent with WHO guidance; See Table 1. [HSE, 2020]

The HSE requires that a fit test is performed by a competent fit test operator prior to wearing an FFP respirator to ensure that it fits the wearers face shape, without creating gaps between mask and face that might allow air to pass unfiltered. FFP respirators with a valve can reduce the overall breathing resistance, heat and humidity build up in the mask. However, these are not suitable for use in preventing the spread of respiratory viruses, such as COVID-19, as the virus can pass through when the valve opens on exhalation [WHO 2020b]

Fluid resistant surgical masks provide a barrier to prevent droplets reaching the wearer's nose, mouth and respiratory tract. Most are not designed to fit closely to the face which means that airborne particles (aerosols <100 microns) could potentially pass through the gap between the mask and the face.

Looking to other respiratory viruses; randomised controlled trials (RCT) comparing the effect of surgical masks and N95 respirators on the rates of acquisition of influenza by healthcare workers mostly report no significant difference in efficacy of the N95 respirators versus the surgical masks [Loeb et al., 2009; HPS, 2020].

**Table 1.** A summary of respirators that are authorised for use in healthcare settings by healthcare personnel (HCP) when used in accordance with CDC recommendations to prevent wearer exposure to pathogenic biological airborne particulates during FFR shortages resulting from the Coronavirus Disease 2019 (COVID-19) outbreak.

Note: Adapted from Rapid Evidence Review – Delivered by HSE for the Government Chief Scientific Adviser (HSE, 2020)

Jurisdiction	Performance Standard	Acceptable product classifications	Standards/Guidance Documents	Protection Factor $\geq 10$
<b>Australia</b>	AS/NZS 1716:2012	P3, P2	AS/NZS 1715:2009	YES
<b>Brazil</b>	ABNT/NBR 13698:2011	PFF3, PFF2	Fundacentro CDU 614.894	YES
<b>Europe</b>	EN 149-2001	FFP3, FFP2	EN 529:2005	YES
<b>Japan</b>	JMHLW-2000	DS/DL3 DS/DL2	JIS T8150: 2006	YES

One cluster RCT did suggest a significant reduction in ‘clinical respiratory illness (CRI)’ associated with the use of non-fit tested N95 masks, compared to fit-tested and medical masks, but the study was underpowered with only 95 cases of CRI (39 laboratory confirmed virus) from 1441 participants in 15 hospitals. There were also significant differences between groups in hospital characteristics [MacIntyre et al., 2011].

There is evidence that suggests that droplet precautions provide adequate protection for staff caring for patients with SARS-CoV-2 who have respiratory symptoms, including coughing and sneezing. A systematic review of 172 observational studies on COVID-19, SARS-CoV-1, and MERS-CoV indicated that policies of at least 1m physical distancing are associated with a large decrease in risk of transmission of infection (adjusted odds ratio - aOR 0.18, 95% CI 0.09 to 0.38). The data also suggests that people, including healthcare workers, are protected by wearing surgical face masks (aOR 0.15, 95% CI 0.07 to 0.34), with eye protection potentially conferring additional benefit (aOR 0.22, 95% CI 0.12 to 0.39) [Chu et al., 2020].

Specific evidence from exposure incidents, although small-scale, suggests that surgical masks are protective. An investigation of 120 contacts, including 17 close contacts, exposed to a case of COVID-19 without aerosol generating procedures, found no evidence of nosocomial transmissions where droplet and contact precautions were applied, including the use of surgical masks [Wong et al., 2020]. A report by Ng et al. from Singapore regarding 41 healthcare workers (HCWs) exposed to a SARS-CoV-2 patient (subsequently laboratory-confirmed) during non-invasive ventilation (NIV), emergency intubation and extubation, found that no HCWs developed COVID-19. A surgical mask was worn by 85 % of the HCWs [Ng et al., 2020].

Although most countries recommend droplet precautions and the use of fluid resistant surgical masks when providing routine care of patients with COVID-19, some recommend routine use of FFP respirators. However, evidence that widespread use of respirators provides better protection and reduces acquisition of COVID-19 by healthcare workers is inconclusive. [ARHAI Scotland, 2020]

## To understand SARS-CoV-2 transmission, we need to understand aerosols

Different types of evidence can be used to understand transmission routes of respiratory viruses, for example: epidemiological evidence of patterns of transmission or absence of transmission from outbreaks, clusters or cases; inference from experiments, animal studies and mathematical modelling to simulate the dynamics of transmission.

- Clinical studies describing routes of transmission are typically from uncontrolled studies and therefore cannot rule out the possibility that infection was due to routes other than that claimed in the report, or that other factors mitigating the risk were in place. There is also a tendency for studies demonstrating evidence of transmission to be more likely to be published than those where no transmission occurred, hence creating publication bias.
- Laboratory-based studies can include controls, but they can only provide evidence for part of the transmission process and demonstrate potential rather than confirmed actual routes of transmission.
- Mathematical models of infection transmission do not provide empirical evidence and are influenced by the assumptions that underpin the parameters used to build them.
- Animal studies are suitable for demonstrating disease and transmission of SARS-CoV-2 but may not be transferable to humans.

Given that none of these sources of evidence provide perfect information, all four types of evidence are required to form conclusions about the transmission dynamics of SARS-CoV-2. While identical transmission cannot be assumed, evidence derived from studies of similar respiratory viruses such as SARS-CoV-1, MERS-CoV and influenza viruses might be relevant to develop understanding of the transmission of SARS-CoV-2.

Sufficient knowledge of particle size and origin relevant to expiratory activity is important to understand virus transmission via the aerosol route [Morawska et al., 2009]. An understanding of how expiratory emissions form within the respiratory system is the beginning of understanding aerosols, which is covered in detail in a review by Seminara et al, 2020. The overview covers many aspects of atomisation, including production due to shear flow over a liquid surface, occlusion of small airways and breakup of liquid sheets outside of the respiratory tract during sneezing [Seminara et al., 2020]. The authors state that overall, the physics involved suggests that the isolated-drop emission picture is inadequate because respiratory liquid drops are formed and emitted embedded in a gas cloud, the presence of which is key to



our understanding of range and persistence of pathogen-laden droplets. Patients infected with upper respiratory tract viruses produce greater numbers of particles in coughs than when they have recovered from their infection [Lee et al., 2019]. The specifics for SARS-CoV-2 remain unknown, partly due to the challenges and heterogeneity in the experimental studies and models conducted over many years. Different expiratory techniques have been used to measure the size distribution of the exhaled droplets and results of different investigations can differ broadly, even by orders of magnitude. An excellent review of the field is provided by Seminara et al. highlighting our limited understanding of the transport processes through which the cloud modifies its composition on moving away from the source [Seminara et al., 2020]. These modifications affect the possible infection mechanisms. Larger droplets tend to settle in the immediate vicinity of the infected emitter, while others are advected away from the source and evaporate at rates dependent on temperature and relative humidity of the emitted clouds.

A higher concentration of droplets is produced during coughing than speaking and expired particles are larger than those produced from speaking or breathing – See figure 2 [Johnson et al., 2011]. The larger particles contain more fluid and potentially more virus. Due to the generation process of coughing particles, they might originate from different places in the respiratory tract and this may influence pathogen load. However, given their larger size, these particles are likely to remain airborne for less time. The heterogeneity of studies is an issue in interpreting this evidence, as many studies only measure small particle sizes and the vast majority report concentration.

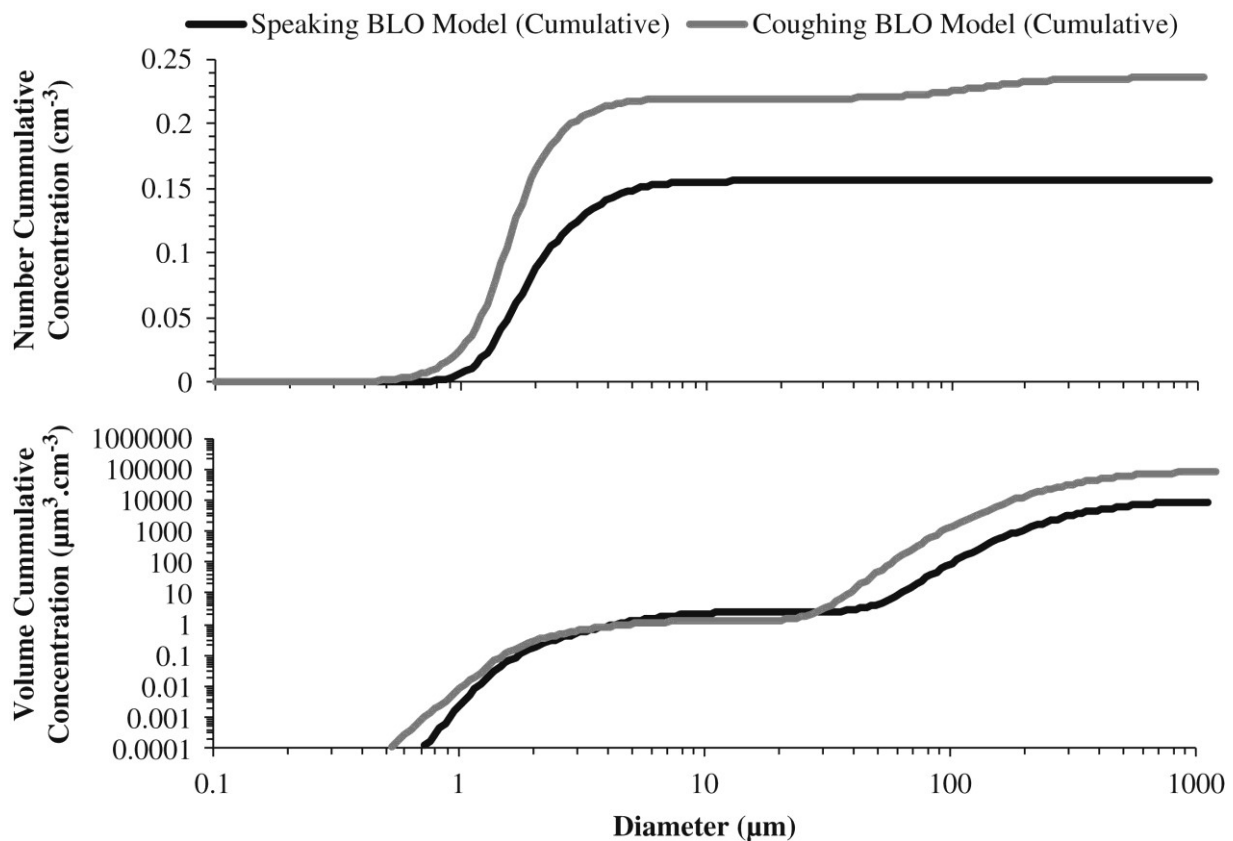
When expressed as volume (or mass) concentration by size, nearly all of the fluid (and virus if derived from liquid of the same concentration) is contained in the larger droplets. See figure 2 below for an example, which shows that 10,000-100,000 times as much liquid is present in droplets greater than 5  $\mu\text{m}$  for speaking or coughing. The competing risks of having more virus in larger droplets ( $>10 \mu\text{m}$ ) at lower concentration versus a higher concentration of smaller droplets with lower viral load ( $<10 \mu\text{m}$ ) are not well understood.

Conventionally, respiratory droplets have been considered to be those particles  $>5\text{-}100 \mu\text{m}$  diameter and their mass causes them to be rapidly deposited [Vejerano & Marr, 2018]. These droplets, if carrying virus, can transmit infection when a susceptible person is in close proximity (1-2 metres). Historically, in clinical and public health contexts, this has been seen as a dichotomy, with proximity being a proxy for droplet transmission [Fennelly, 2020]. In more recent years, there is an appreciation of a continuum of particle size and the occurrence of short-range aerosols with laboratory-based evidence. Various factors must be considered, such as force and volume of exhalation as well as humidity, temperature and airflow in the surrounding environment [Gregson et al., 2020]. Using an expiratory droplet assessment kit (0.5  $\mu\text{m}$  - 20  $\mu\text{m}$ ) on healthy volunteers, Gregson et al. found that breathing, speaking, singing and coughing created particles that had diameters less than 5  $\mu\text{m}$ , but at varying concentrations. As the amplitude of speaking or singing increases, the concentration of particles from speaking and singing increase in parallel. Coughing produced the highest concentration of particles with diameters of less than 5  $\mu\text{m}$ .

Throughout the trajectory, droplets of all sizes settle out or evaporate at rates that depend not only on their size but also on the degree of the turbulence and speed of the gas clouds, coupled with the properties of the ambient environment (temperature, humidity and airflow). Particles with diameters up to 100  $\mu\text{m}$  (and potentially higher) can be inspired and retained in the respiratory tract [James et al., 1994]. The site where they deposit may determine the viral dose required and the severity of infection, as seen in influenza [Fennelly, 2020].

**Figure 2.** Cumulative number and volume concentration size distributions for speaking and coughing according to the BLO model of the aerosol concentration size distributions for speaking and coughing, are summarised by Johnson et al. (2011)

Note: From Modality of human expired aerosol size distributions, by Johnson et al. (2011)



## Evidence base for SARS CoV-2 transmission routes

High viral RNA load in the saliva of symptomatic patients has been reported, reaching  $7 \log_{10}$  copies  $\text{ml}^{-1}$  [To et al., 2020; Wolfel et al., 2020; He et al., 2020] with 60% of patients (3 out of 5 tested) showing positive for culture of SARS-CoV-2 virus [To et al., 2020]. Coughing is a symptom of COVID-19 [WHO 2020a., Docherty et al., 2020] and can generate aerosols, thus coughing and other expiratory activity studies and observations are important to consider.

Schijven et al. developed an exposure assessment model (modelling study) to estimate the numbers of SARS-CoV-2 particles expelled during breathing, speaking, coughing and sneezing by an infected person in an unventilated indoor environment, and subsequent inhalation by one or more persons. The scenarios (e.g., low and high scenarios for coughing) studied encompassed modelling of a range of virus concentrations, room sizes and exposure times. The results revealed that the highest volume of particles occurred during a sneeze, followed by cough and speaking loudly for 20 minutes and finally, breathing for 20 minutes [Schijven et al., 2020].

Transfer of infectious particles may occur directly or be the result of indirect, hand-mediated, transfer of the virus from contaminated surfaces or fomites (inanimate objects) See figures 3 and 4. Despite consistent evidence as to SARS-CoV-2 contamination of surfaces and the survival of the virus on certain surfaces, there are no specific reports which have directly demonstrated fomite transmission.

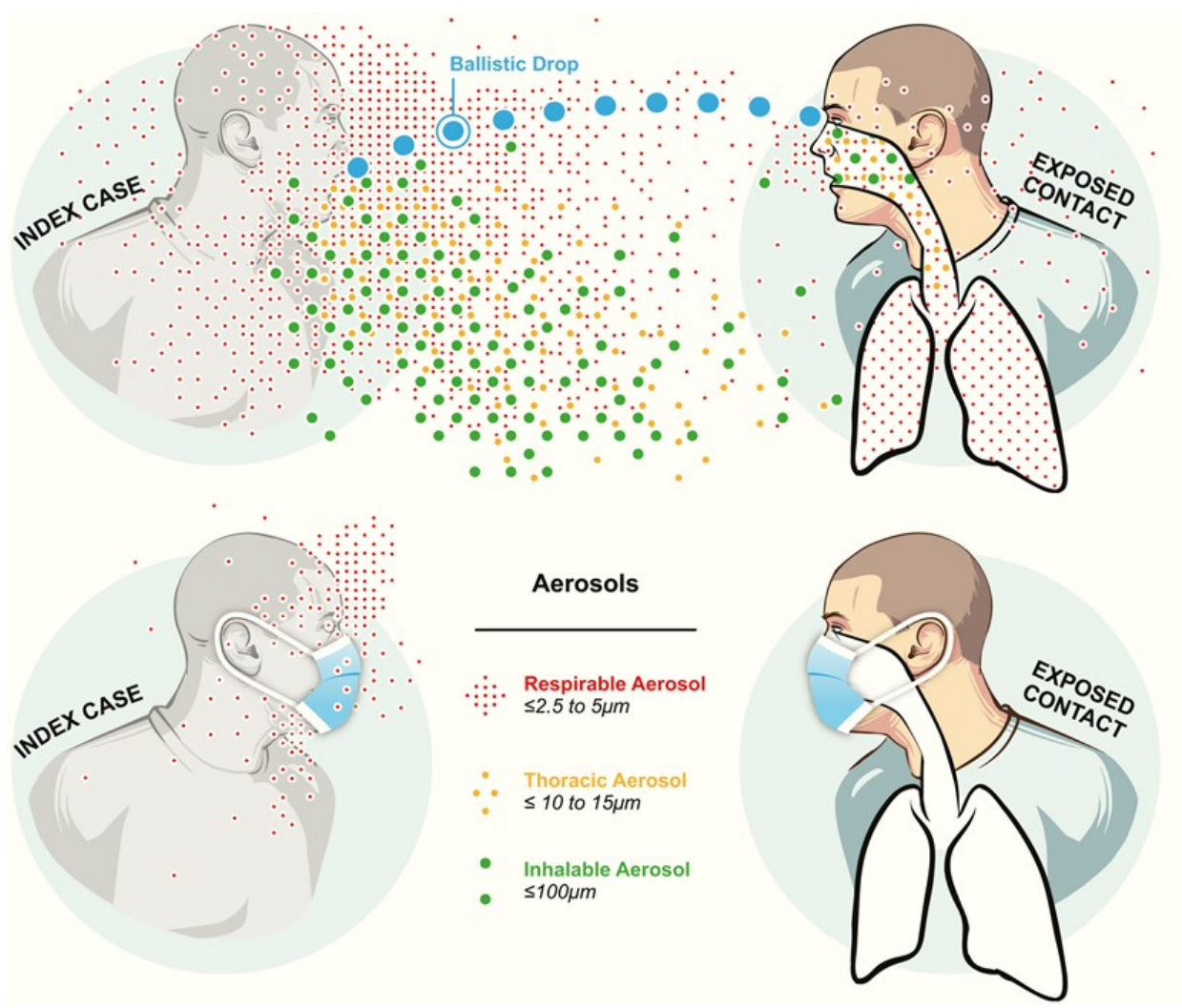
People who come into contact with potentially infectious surfaces often also have close contact with the infectious person, making the distinction between respiratory droplet and fomite transmission difficult to discern. However, fomite transmission is considered a likely mode of transmission for SARS-CoV-2, given consistent findings about environmental contamination in the vicinity of infected cases and the fact that other coronaviruses and respiratory viruses can transmit this way. For example, there are a small number of reports of community outbreaks in crowded, indoor spaces where transmission via aerosols is a possible explanation. However, the transmission in these clusters could also be explained by droplet or fomite transmission, especially in the context of prolonged exposure time, and the absence of physical distancing, masks or emphasis on hand hygiene - mitigation methods that reduce droplet transmission [CDC, October 2020].

Studies of particle emissions from the respiratory tract of humans are based on laboratory experiments. Although there is some evidence that aerosols carrying virus particles can survive for several hours when generated in artificially high concentrations [Van Doremalen et al., 2020], these experiments are not able to demonstrate that they have the capacity to transmit infections or define the infectious dose. Some studies conducted in healthcare settings where COVID-19 patients were being cared for have identified SARS-CoV-2 RNA in air samples but in very low quantities and none of the studies were able to demonstrate that virus detected in air samples was viable [Santarpia et al., 2020; Chu et al., 2020; Zou et al., 2020].

In a hospital-based study, Moore et al. sampled across 8 hospitals during the first wave of the pandemic in England [Moore et al., 2020]. This preprint describes environmental contamination of frequently touched surfaces, therefore emphasising the role of regular cleaning of surfaces including vital signs equipment e.g., pulse oximeters. The aerobiology team also sampled air and, from 55 air samples, 4 were positive for SARS-CoV-2 by PCR at low concentration, which was not culturable. The authors cite a number of limitations to their study, such as short air sampling times of 10 minutes. Three of the four positive samples were taken in close range to patients receiving continuous positive airway pressure (CPAP) or oxygen via a Venturi mask. The fourth was in a cohort bay at day 8 of illness, with laboratory-confirmed SARS-CoV-2 infection. However, 30-40 minutes before the sampling was carried out there was an emergency call, which had resulted in increased staff activity in the cohort bay, but no cardiopulmonary resuscitation (CPR) or intubation performed. The authors postulate that the increase in staff activity may have facilitated the dispersal of airborne particles.

**Figure 3.** A diagrammatic representation of the modes of transmission of respiratory viruses.

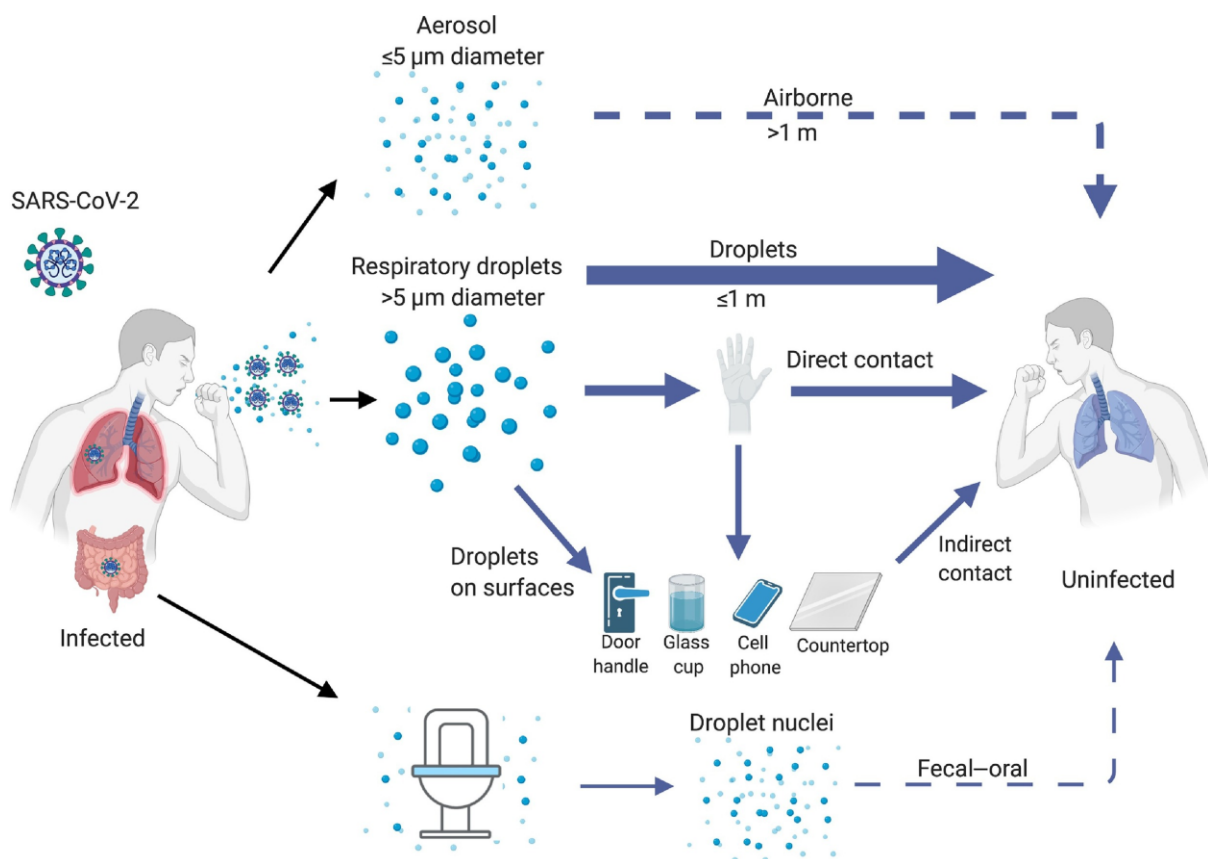
Note: Adapted from A Rosetta Stone for Understanding Infectious Drops and Aerosols by (Milton 2020)



**Figure 4.** Proposed Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Transmission Routes.

The ongoing COVID-19 pandemic has resulted in numerous accounts of different transmission routes between humans. Droplet transmission ( $>5\ \mu\text{m}$ ) is the most pronounced and heavily implicated mode of transmission reported during the pandemic. Direct contact spread from one infected individual to a second, naïve person has also been considered a driver of human-to-human transmission, especially in households with close interactions between family members. The contagiousness of SARS-CoV-2 after disposition on fomites (e.g., door handles) is under investigation, but is likely a compounding factor for transmission events, albeit less frequently than droplet or contact-driven transmission. Both airborne and fecal–oral human-to-human transmission events were reported in the precursor SARS-CoV epidemic but have yet to be observed in the current crises. Solid arrows show confirmed viral transfer from one infected person to another, with a declining gradient in arrow width denoting the relative contributions of each transmission route. Dashed lines show the plausibility of transmission types that have yet to be confirmed. SARS-CoV-2 symbol in ‘infected patient’ indicates where RNA/infectious virus has been detected.

Note: From Mechanisms of SARS-CoV-2 Transmission and Pathogenesis (Harrison, Lin & Wang, 2020)



## Role of Ventilation

Airborne respiratory particles are rapidly diluted and dispersed by the movement of air. Evidence from community outbreaks and aerobiology studies indicates that ventilation may play a role in transmission. The risk of transmission is therefore likely to be increased by close contact in small, poorly-ventilated spaces for a prolonged period of time [ECDC, 2020b]. The evidence for the role of ventilation in facilitating and controlling transmission has been reviewed by the Scientific Advisory Group for Emergencies (SAGE) Environmental and Modelling Group and summarised below with levels of confidence indicated by the expert advisory group [SAGE EMG, 2020].

- Ventilation is an important factor in mitigating against the risk of far-field (>2m) aerosol transmission but has no impact on other transmission routes (high confidence). The importance of far-field aerosol transmission is not yet known, but evidence suggests it is a risk in poorly ventilated spaces (medium confidence).
- Far-field aerosol transmission depends on the interaction of multiple factors including the viral emission rate, the ventilation rate, the duration of exposure, the environmental conditions and the number of occupants (high confidence).
- Activities that may generate high levels of aerosol (singing, loud speech, aerobic activity) are likely to pose the greatest risk; in some spaces, even enhanced ventilation may not fully mitigate this risk (medium confidence).
- Virus survival in air decreases with increasing temperature and humidity. In most environments this effect is likely to be less important than the ventilation rate, however environments with low temperature and low humidity (e.g. chilled food processing, cold stores) may pose an enhanced risk (medium confidence).
- Providing the ventilation rate remains the same, increasing the occupancy of a space increases the probability of airborne transmission by four-fold. Exposure risk may be further increased if distances between people are reduced to <2m. (medium confidence).
- Measurements of elevated CO<sub>2</sub> levels in indoor air are an effective method of identifying poor ventilation in multi-occupant spaces. In low occupancy or large volume spaces a low level of CO<sub>2</sub> cannot necessarily be used as an indicator that ventilation is sufficient to mitigate transmission risks (medium confidence).
- Ventilation should be considered as part of a hierarchy of risk controls approach.
- Source control measures such as restricting or reducing duration of activities and enhanced use of face coverings should be considered alongside ventilation for reducing far-field aerosol transmission risks.
- Assessing ventilation in many environments requires engineering expertise, and mitigation measures are setting-specific, taking into account the nature of the building and users, ventilation type, length of exposure and activity. Unlike distancing and hand washing, ventilation requirements cannot easily be distilled into one simple approach that everyone can follow.

- Any changes to ventilation must consider other negative consequences including financial, energy use, noise, security and health and wellbeing impacts from thermal discomfort and exposure to pollutants.
- The effectiveness of ventilation in many environments is strongly influenced by user behaviour (high confidence). Clear messaging is needed about the reasons why good ventilation is important and how to effectively operate ventilation systems or achieve good natural ventilation

Fallow times have been utilised in anaesthetic rooms and dental surgeries for example. A recent dental review has resulted in a revision and shortening of the fallow time from 60 minutes in dental settings to 20 minutes if 10-12 air changes per hour in a single treatment room is possible. In addition, dental professionals can calculate the necessary fallow time between procedures with a free online tool. The new guidance from the College of General Dentistry (CGDent) and the Faculty of General Dental Proactive (FGDP UK) - published on 2 October 2020 in the second version of 'Implications of COVID-19 for the Safe Management of General Dental Practice: A Practical Guide' - was based on a 25 September review of the evidence relating to AGPs that was conducted by the Scottish Dental Clinical Effectiveness Programme (SDCEP) [SDCEP, 2020].

## Aerosol generating procedures

The term 'Aerosol Generating Procedures' (AGPs) is defined as medical procedures that have been reported to be aerosol-generating and consistently associated with an increased risk of aerosol transmission [WHO, 2014]. This played a pertinent role during and after the SARS-CoV-1 epidemic, when certain medical procedures were considered to be of higher risk of producing an aerosol than coughing. As a result, the guidance recommended applying environmental (e.g. patient placement) and engineering (e.g. ventilation) controls, and use of PPE (respiratory and eye protection, gloves and gowns) during specific aerosol-generating procedures consistently associated with an increased risk of pathogen transmission, performed on patients with acute respiratory infections of concern.

There are limitations to those reports, including where contact transmission may have played a greater role. The Morbidity and Mortality Weekly Report (MMWR) of a Canadian cluster of HCW infections associated with caring for one severely ill case of SARS-CoV demonstrates how difficult it is to know for sure where the highest risk lies [MMWR, 2003]. The proximity and time the susceptible person is exposed to the patients with respiratory distress may be stronger determinants of risk than the procedures.

A systematic review of studies related to SARS-CoV-1 concluded that, "a significant research gap exists in the epidemiology of the risk of transmission of acute respiratory infections from patients undergoing aerosol generating procedures to health care workers, and clinical studies should be carefully planned to address specific questions around the risk of transmission in these settings." [Tran et al., 2012].

Currently, infection prevention & control (IPC) guidance treats all high risk AGPs as a single level of risk. Harding et al. highlight that there likely is a hierarchy of AGPs in

the sense that each conveys a different degree of risk of transmission [Harding et al., 2020]. Jackson et al. in a rapid review clearly show the differences across countries in which procedures are considered to be aerosol generating during this pandemic, and call for more research into this area [Jackson et al., 2020]. One recent piece of published research by Brown et al. using air sampling around a patient during a controlled anaesthetic intubation, suggests that in that setting, intubation does not generate more aerosol than coughing [Brown et al., 2020]. There are limitations to this research which raises the urgent need to define the evidence around medical procedures and risk of aerosol generation. This review, however, is focussed on a sub-set of procedures - as yet unclassified for aerosol risk - where current professional societies have raised concerns.

## Conclusion

Respiratory particles in the form of droplets and aerosols, which are expelled from the respiratory tract during speaking, breathing and coughing, contribute to transmission of SARS-CoV-2. The epidemiological evidence suggests that the risk of transmission is predominantly from short range exposure, from a person who generates significant amounts of virus. The risk of transmission associated with aerosols is influenced by a range of factors including the concentration and mass of particles emitted, the viral load, the proximity and duration of exposure and the circulation of air in the environment.

The Hierarchy of Controls [CDC, 2015], underpins infection prevention and control and recommends using strategies that reduce the risk of exposure to the virus, rather than only relying on the use of PPE. Such strategies include eliminating the hazard by avoiding admission/treatment of people with active infection and using testing to segregate patients with the infection. Engineering controls such as physical barriers, and administrative controls such as procedures to facilitate physical distancing, are also included in the hierarchy. These strategies reduce the risk of transmission from the approximately 20% of people with SARS-COV-2 who are asymptomatic. The risk of encountering an asymptomatic COVID-19 patient if appropriate engineering and administrative controls are in place is low, see table 2.

Patients with SARS-CoV-2 infection who are breathing, talking or coughing generate both respiratory droplets and aerosols, but FRSM (and where required, eye protection) are considered to provide adequate staff protection and there is evidence to support this conclusion. High risk AGPs are medical procedures where there is consistent evidence to suggest an association in infection transmission. Medical procedures which provoke coughing or heavy breathing would need to be associated with an increase in aerosol generation beyond that which would occur during the routine care of any COVID-19 patient.



**Table 2.** Estimated risk of patient being asymptomatic at time of treatment.  
Assumes that 20% of cases are asymptomatic

Note: Adapted from Mitigation of Aerosol Generating Procedures in Dentistry – A Rapid Review, SDCEP (2020)

Average no. cases in population (prevalence) per 100,000	Estimated no. cases that are asymptomatic in population (prevalence)	
	Per 100,000	Equates to 1 patient in
5	1	100,000
10	2	50,000
50	10	10,000
100	20	5,000
400	80	1,250
500	100	1000

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