



## REVIEW ARTICLE

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# Status: nosocomial transmission and prevention of SARS-CoV-2 in a Danish context

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The unexpected pandemic with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has challenged the healthcare sector as regards preventing and controlling the virus from spreading between patients and hospital personnel. The massive spread of the pandemic has led state authorities to introduce restrictions on society and public behavior unprecedented in modern times. First, we describe the Danish effort regarding standard precautions, personal protective equipment, and disinfection in the healthcare setting with Denmark as an example. As regards, the number of coronavirus disease 2019 (COVID-19)-related hospital submissions, deaths, and infected healthcare workers in Denmark is not the hardest hit country compared with others. This cannot be explained by the hardness of the restrictions alone. Several aspects concerning the person-to-person spread of SARS-CoV-2 are not fully understood and require more experimental studies. The dogma is that virus transmission happens through either respiratory droplets or contact routes. However, it is likely not the whole truth, as we describe scenarios where droplets and/or direct contact cannot alone explain how all patients were infected. Aspects of the physiology of airborne transmission are considered, as several parameters are in play beyond particle size and respiratory rate. These are ozone concentration, ambient temperature, and humidity. In a hospital environment, these factors are not necessarily all controllable, making infection prevention and control a challenge.

Key words: Nosocomial transmission; SARS-COV-2; COVID-19; droplet; airborne transmission.

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## INTRODUCTION

The emergence of new coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, Hubei province of China, back in November 2019 was the beginning of a new pandemic with spread to many countries worldwide. SARS-CoV-2 is the causative agent behind the coronavirus disease 2019 (COVID-19) [1].

Early in the infection, the virus can be detected both in the upper part of the respiratory tract and later on in the lower parts and can be detected in both parts of the airways [2]. The virus can also be identified in samples from the throat, conjunctivae, sputum, blood, urine, and feces. In fact, the concentration of virus RNA in feces is high [1].

The virus was initially named 2019-nCoV but renamed SARS-CoV-2 due to its relationship with SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV), also zoonotic virus. Since the origin of SARS-CoV-2 pandemic, the countries have handled the pandemic differently. National lockdown of the society in terms of closure of shopping centers, schools (in fact physical distancing), contact tracing, and testing both national and international travelers, and international travel restrictions and bans was imposed. Some countries have experienced the SARS-CoV-1 back in 2002. Especially, Hong Kong was hard hit by SARS-CoV-1 with 1755 SARS cases and 298 deaths [3]. The prevention and control measures undertaken in Denmark have been focusing on hand hygiene, social distancing, droplet precautions, and lockdown of the society, working at home, and cancelation of gatherings. Additional

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step in terms of wearing mask in public is mandatory.

As writing, the number of cases and deaths globally has reached 163,959,840, respectively, and 3,348,241, and in Denmark, 262,159 cases and 2499 deaths [4]. On December 31, 2019, the Chinese authorities reported to the World Health Organization (WHO) that an epidemic was under development. On March 11, 2020, WHO declared that the disease was a pandemic [5].

SARS-CoV-2 is a spherical, enveloped, non-segmented positive single-stranded RNA virus with protein spikes in the membrane. The nucleocapsid protein encapsulates the RNA and protects it. The envelope is lipid bilayer membrane, which can be susceptible to destruction by dry heat, organic solvents, and detergents [6]. The virus uses the angiotensin-converting enzyme 2 (ACE2) receptors to enter the human cells, and the protease TMPRSS2 (transmembrane protease serine type 2) facilitates the further internalization process. The presence of ACE2 receptors is ubiquitous, since the receptor is present in the central nervous system, conjunctivae, gastrointestinal system, lung, heart, kidney, and testes [7]. The size of SARS-CoV-2 is 120 nm. Knowledge about the transmission route is essential to prevent the virus from spreading [7].

The SARS-CoV-2 belongs together with SARS-CoV and MERS-CoV to the betacoronavirus genus. The genome sequence homology between SARS-CoV and SARS-CoV-2 is 80% and between SARS-CoV-2 and MERS-CoV is 50% [7]. The genome of SARS-CoV-2 has 96.2% similarity to CoV-TaTG13 from bats [8].

The respiratory illness, COVID-19, has a span in symptomatology from asymptomatic to severe pneumonia with acute respiratory distress syndrome. The median incubation period is 5.1 days, and the majority of infected patients have symptoms within 12 days [9]. The basic reproduction number ( $R_0$ ) is estimated to be 2.2–2.6 [10]. The mortality of COVID-19 seems lower as compared to SARS and MERS, that is, 2.1%, 9.2%, and 34.4%, respectively. The mortality rate is highest among elder and patients with comorbidity [10].

During the initial stage of the pandemic, Denmark and other countries had no official standard of care for neither oxygen nor medical treatment for COVID-19. The treatments were based on experiences from China and Italy. Initially, the treatment consisted of high flow nasal oxygen or ventilation. After some months, this was combined with dexamethasone and antiviral therapy with remdesivir [11, 12]. Anticoagulation therapy was added due to thrombosis and coagulation abnormalities in patients with severe COVID-19 disease [13].

## MANAGING THE COVID-19 IN THE HEALTHCARE SYSTEM

In the beginning, the overall strategy in Denmark was a containment policy, which aimed to delay the epidemic by means of diagnostics, isolation, and quarantine of patients and close contacts. When WHO in Marts 2020 declared a pandemic, the Danish Health Authority has launched a mitigation strategy with the aim of preventing the spread of infection to healthcare workers (HCW) and patients [14].

The medical professional guidance has been conducted by the Danish Health Authority, Statens Serum Institut (SSI), and the National Center for Infection Control (CEI). These three organizations have published guidelines and recommendations aimed to prevent the virus to spread, protect individuals at risk of severe disease acquiring the virus, and that the impact on the healthcare system due to the increased demand was not overstretched.

A central discussion was how far droplets could travel through air. According to WHO, the distinction between droplets and aerosols begins below 5  $\mu\text{m}$ . However, some authors use other droplet size cutoffs and imply that droplets are able to stay long in the air without evaporation [15]. WHO recommends contact and droplet precautions for HCW dealing with suspected COVID-19 patients. In contrast, US CDC had a more careful approach, recommending airborne precautions for HCW and equip the patients with masks. European CDC joined the recommendation by WHO. But one must consider that although the droplets have a certain size when exhaled from the airways, the droplets can vary in change size due to temperature, velocity, and humidity [16].

First, the Danish guideline on handling COVID-19 was released on January 15, 2020. The infection control procedures were similar to infection control procedures related to patients suspected for MERS. When patients were admitted to the hospital, they were isolated in single rooms. Patients and all hospital employees were required to wear personal protective equipment (PPE). Initially, the recommended PPE was gloves, disposable gowns, filtering facepiece (FFP3) masks, face shield, and goggles. The Danish Health Authority eventually relaxed the recommendation for the use of FFP3 masks, in juxtaposing FFP2 and FFP3 masks during clinical procedures of high risk, as did they temporarily dispense from the 3 h' time limit for use of the two masks during the peak of the Danish epidemic. In cleaning the hospital area, the recommended products were water and soap, alcohol, or a chlorine solution of a minimum of 1000 parts per

million. Cleaning staff were required to wear PPE when cleaning and managing hospital waste [17].

In Denmark, the isolation of the COVID-19 patients is discontinued either if the patient has been symptom-free for 48 h or in the case of the intensive care unit patient when the patient is fever-free without antipyretics for 48 h and has two negative SARS-CoV-2 nucleic acid amplification tests from both pharynx and trachea 24 h apart [18]. This differs from the WHO guideline [19]. However, the experiences in the Danish health sector have shown that the guideline is highly operational.

Since January 15, 2020, these guidelines have been updated continuously based on knowledge about the disease, development of the pandemics, and experiences from Denmark and abroad, together with guidelines from WHO and European Centre for Disease Prevention and Control (ECDC). The last version was published on January 22, 2021.

In an attempt to control the pandemic, the Danish Health Authority also has conducted contact tracing and launched a national contact tracing app, which the user can activate, when tested positive. The app informs other users, if they have been in contact with the person for more than 15 min at a distance of 1 m [20]. The contact tracing was in the beginning based on that all individuals who were tested positive for SARS-CoV-2 were asked to track down recent contacts with other persons, so they could be tested 4, 6, and 8 days after the day of contact. On May 12, 2020, the Danish Health Authority took over the responsibility for tracking and contacting close contacts to persons tested positive for COVID-19. Whether these initiatives have been successful is difficult to substantiate scientifically, since no data are available.

On October 2, 2020, the Danish Health Authorities released new guideline regarding the spatial distance in public and recommended a distance of at least 1 meter between people and 2 m in specific cases [21]. Furthermore, the guideline took into consideration that under certain conditions such as crowded indoors settings with poor ventilation and recirculation of the air, the risk of infection would be increased. In the guideline, the Danish Health Authorities introduced the concept  $R_e$ .  $R_0$  stands for the basic reproduction number and is pivotal for the political decision makers.  $R_0$  represents the number of secondary cases due to a primary case in the absence of immunity or intervention.  $R_e$  or  $R_t$  (also known as effective R or varying R) is the average number of secondary cases per infectious case, when initiatives have been launched to curb the pandemic. A pandemic will continue for  $R_0 > 1$  and peter out for  $R_0 < 1$  [22, 23]. SARS-CoV-2

pandemic has been characterized by asymptomatic cases. It is estimated that over 80% of the cases are asymptomatic [24]. The contact rate in the asymptomatic group influences the  $R_0$  because their activity is normal in contrast to symptomatic persons who self-isolate. Intensive testing and trace strategy can provide an estimate of the distribution between asymptomatic cases and symptomatic cases and, furthermore, of course provide the opportunity of isolation of “silent spreaders.” Srinivasa and coworkers emphasize that the calculation of  $R_0$  or  $R_t$  is difficult and may not be able to capture the real spread. In fact, miscalculation can lead to underestimation of the true value and that testing and trace campaign should be very extensive and thorough [25]. Moreover, in the former Danish guideline, it was emphasized that there is no scientific documentation for  $R_0$  like measles.

On October 29, 2020, the Danish Health Authority expanded the precaution with wearing masks in public. Concerning the healthcare sector, a principle of caution demanded the use of masks, when moving in common areas. The rule is still maintained [26].

Since ultimo January 2020, Denmark has conducted 29,700,000 PCR tests with 262,159 confirmed infections and 2499 (0.95%) deaths (May 12, 2021) [27]. Danish Health Authority embraced the WHO mantra of mass-scale testing of the population, but initially struggled with the PCR test capacity, because of world shortage of reagents, kits, and cartridges. The PCR test capacity has been continuously expanded due to a variety of in-house analyses and help from the Danish industry, together with the implementation of antigen test provided by private companies. In Denmark, the test capacity has been increased, so it is possible daily to conduct 440,000 antigen tests and 220,000 PCR tests [27]. To prevent nosocomial transmission, Danish Health Authority recommends screening patients at hospital admission if expected stay > 24 h [28].

Regarding success at containing SARS-CoV-2, Taiwan has caught the attention, since the country has 1128 cases and 12 deaths. It is important to note that Taiwan is harboring 24 million people [29]. The reason for this success can be ascribed to the history of SARS-CoV-1, which forced the Taiwanese government to increase the resiliency of the society by strengthening the institutional infrastructure and healthcare system in terms of establishment of National Health Command Center (NHCC). Two months ahead of the announcement of the pandemic by WHO, the Central Epidemic Command Center (CECC) of NHCC on January 20, 2020, launched 124 action items including

border control, travel restriction, case identification, contact tracing, and quarantine rules. In addition, increased investment in isolation wards and negative pressure rooms, after Taiwan, was hidden just as hard as China and Hong Kong back in 2003 by SARS-CoV-1 paid off. Furthermore, the public close-up on the initiative and the population-based intervention in terms of social distancing and wearing masks were part of the culture due to the experience of first SARS outbreak. Generally, the Taiwanese authorities were proactive, and lockdown, school closures, and restaurants were not a part of the strategy [30].

In Beijing, a second outbreak began in June 2020 and was closed in July comprising 335 cases. The strategy was sensitive surveillance since only one case triggered the system and immediate response in terms of case finding, contact tracing, isolation of cases, and close contacts. The effort in Beijing lowering the  $R_0$  [31].

In summary, to curb the pandemic the Danish Health Authority has increased the test capacity providing the possibility to test nearly 10% of the population daily, despite that  $R_e$  is fluctuating and close to 1. In addition, described precautions for droplet and contact-related infection are in line with the recommendation from WHO. These recommendations are based on the presumption that the transmission is due to primarily droplet transmission, but is this framework still consistent with the scientific literature?

## TRANSMISSION

It is well established that respiratory droplets and contact routes are the main contributors to the spread of the virus. The transmission routes are just like SARS-CoV-1 and MERS-CoV [32]. Several aspects regarding the spread of the SARS-CoV-2 virus are not fully understood [33]. Furthermore, indirect contact also occurs, when hands get in contact with surroundings contaminated with secretion from nose, mouth, and eyes from infected person [32].

There is still an ongoing discussion whether the transmission route can be airborne too, and if so, how far can the virus travel. Different studies have tried to shed light on this problem with different experimental settings. Understanding the transmission routes is important, since the infection control recommendations are based on this.

### Terminology

When breathing, talking, sneezing, laughing, singing, and coughing, the virus is released as droplets

or *aerosol*. Based on the study of tuberculosis transmission back in the 1930s, William F. Wells introduced the dichotomy: large droplets vs. small droplets. This simplicity has been the prevailing view since then and essential for the recommendations from the governmental healthcare institutions. The dichotomy is based on the size of the droplets and the distance they can travel [34]. WHO uses a cutoff limit of 5  $\mu\text{m}$  to differentiate between aerosols and droplets. Furthermore, the word aerosols has been used, but the definition is not well established. According to Tellier, aerosols are liquid or solid particles suspended in air [35]. Jones and Broseus define aerosols as Tellier with the addendum that the particles differ in size [36]. Bourouiba concludes that aerosols and droplet nuclei are used synonymous [34] and they are suspended in the air for longer time without evaporation providing the possibility for reaching and infecting a susceptible person at a longer distance. Respiratory particles are composed of water,  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Cl}^-$ , lactate, and glycoproteins. Evaporation is due to the difference in water vapor pressure around the particle surface and the ambient air [16]. Prather and coworkers argued that the terminology must be clarified including the size of the particles [37], since size is determining the distance to travel.

In short, the airborne transmission is characterized by particles below 5  $\mu\text{m}$  and travel distance longer than 1 m, in contrast to the dogma of droplet transmission where a working distance longer than 1 m is considered safe. Below 5  $\mu\text{m}$ , the droplets can reach the alveoli, and close standing persons can have mouth mucosa and eyes exposed. Larger droplets fall very quickly to the ground without evaporation. Moreover, the particles may be able to travel more than 1–2 m, remain in the air for longer time, and contain infection-competent virus [15, 34, 38, 39].

### Contaminated surfaces

SARS-CoV-2 persistence on surfaces under different conditions of temperature and humidity may also play a central part in transmission of the virus both in a clinical setting and in the public space. The decay of SARS-CoV-2 on surfaces is correlated so that higher temperature and relative humidity reduce the half-life of the virus [40]. This implies not only that winter may facilitate epidemics, but also that both frozen and chilled food products may similarly pose an increased risk of SARS-CoV-2 transmission. The re-emergence of SARS-CoV-2 outbreaks has been reported in Chinese cities (Beijing, Dalian, and Shenzhen), where the sources have been reported to be frozen and chilled fish

products from seafood market, seafood processing companies, and on the outer packing of imported chilled products [41].

### Size distribution

The investigation of the size distribution is dependent on the technology available and poses several challenges. The reference point has been studied from the 1920s and 1940s. Studies concluded that most droplets were in the super-micrometer size due to the lack of sensitivity to the small droplets. The early studies by Duguid and Older had sensitivity limitations due to the technology and found that 95% of particles were below 100  $\mu\text{m}$ , when coughing or sneezing. In fact, the greatest part was in the range from 4 to 8  $\mu\text{m}$ . Papineni and Rosenthal using an optical particle counter found that 80–90% of particles were below 1  $\mu\text{m}$  [16, 42]. New technologies such as expiratory droplet investigation system (EDIS), where the volunteer is placed in a wind tunnel, provide new insight into the different parameters (temperature and humidity) [43]. The particle sizes consist of a continuum of different sizes, why the protection of health workers is important [44].

### Numbers of droplets and velocity

Expiratory activity constitutes breathing, talking, singing, sneezing, laughing, and coughing, which all release droplets or aerosols with different numbers and velocities. The velocity of droplets expelled by breathing is estimated to be 1 m/s and talking 5 m/s. When sneezing, the velocity was 20–50 m/s [45]. Zhu et al. [46] observed that during coughing the droplets would be expelled with 22 m/s with a distance longer than 2 m. Coughing releases, according to Dhand and Li [47], 3000 droplets, a sneeze about 40,000 droplets.

### Distance to travel

The crucial point is whether the droplets travel longer than 1–2 m. When the droplet is expelled, its initial velocity, ventilation patterns, temperature, and humidity would influence how far they travel. These factors influence on the distance that droplets can reach. Bourouiba found that droplets loaded with pathogens of all sizes could travel as far as 7–8 m [48]. Günter and colleagues investigated an outbreak in a large meat processing complex in Germany, where a single index patient gave rise to the outbreak. Up to 60% of the coworkers acquired the virus in the first outbreak and subsequent second outbreak. The outbreak was caused by a single

genotype. Günter and colleagues concluded that transmission occurred within 8 meters due to analyzing the working process, where the employees were working close together. Furthermore, contributing factors such as low temperature, low air exchange, and constant air circulation, together with closed contact, facilitated the airborne transmission [49]. Regarding breathing and talking, the distance is probably within 1–2 m. However, people are not walking around coughing and sneezing. And if doing so, hopefully they are protecting their surroundings by sneezing and coughing in the sleeve. Of course, cough and sneeze are not the most important, since breathing and talking are the most frequent respiratory activities.

### Epidemiological studies

According to Chinese observations, the SARS-CoV-1 was detectable in ventilation systems in hospital rooms of patients with COVID-19 [50]. Furthermore, in some local outbreaks the transmission only by droplets has been questioned. In addition, drawing analogies back in history with SARS-CoV-1 in Hong Kong apartments indicates clearly that coronavirus had the capacity to long-distance spread through air [51]. Also, transmission in aircraft has been observed [52]. Furthermore, Li et al. described an outbreak with SARS-COV-2 in Restaurant X in Guangzhou in China involving three families (named A, B, and C), which were not associated. Family A came from Wuhan, Hubei, and one of the members was infected with SARS-CoV-2. The three families were placed at different tables close to each other on a line in front of a ventilation system. Three members of family B and two members of family C were infected; furthermore, four persons from family A became infected. None of the remaining guests and service staff were infected ( $N = 68$ ). Li et al. had access to video surveillance camera and could confirm that the persons at the three tables were not in close contact. They also examined the travel history, exposure time, genetic analysis of virus, and weather conditions. They conducted two tracer gas experiments to identify the airflow pattern. They concluded that droplet transmission could not alone explain the outbreak, since the distance between the index person and some of the other infected persons was greater than the 4.6 m. They suggested that airflow from the air conditioner could have transported the droplets the long distance [53].

According to WHO, a super-spreader is defined as an infected person, who infects more people than usual. A super-spreading event is defined by  $R_0$ , where an infected person transmits the virus to

more people than usual, in case  $\geq 8$  persons [54]. In an attempt to explain the phenomenon, it has been suggested that both asymptomatic persons and immunocompromised persons unable to control virus multiplication could release virus in large quantities during social arrangements, as the effect of shouting and heavy breathing could have an influence [54]. Stadnytskyi et al. observed by using laser light that loud speech releases  $1000 \text{ s}^{-1}$  to  $10,000 \text{ s}^{-1}$  with size  $10\text{--}100 \mu\text{m}$  and airborne lifetime for some at least 30 s. Furthermore, if evaporation occurs the airborne lifetime expands [55]. The virus RNA load in oral fluid is measured to  $2.35 \times 10^9$  copies per milliliter [2]. It is estimated that the probability is 37% that a droplet with diameter of  $50 \mu\text{m}$  contains at least one virion [55]. In line with these observations, Edwards et al. found that by breathing persons could be classified into low producers expelling  $< 500$  droplets per liter over six hours and super-producers exhaling  $> 500$  droplets per liter over 6 h [56]. Airborne transmission could offer an explanation for the super-spreaders and super-spreading events [15].

The distinction is not clear-cut, but epidemiological studies can be used in both ways. When analyzing the data, it will often be difficult to conclude whether people have been in close contact or not. When breathing (mouth and nose), talking, and coughing, the size of the particles in the aerosols is by optical particle counting determined to be below  $1 \mu\text{m}$  [42].

Some argue against the theory about airborne transmission based on the fact that the reproduction number ( $R_0$ ) is 2. Diseases such as measles with airborne transmission have  $R_0$  from 6 to 19 [57]. The distinction is not clear-cut, but epidemiological studies can be used in both ways. When analyzing the data, it will often be difficult to conclude whether people have been in close contact or the contacts were more distant. Furthermore, low  $R_0$  does not preclude airborne transmission.

Deposited virus-containing secretions may also be re-aerosolized by activities such as walking, cleaning the room, and door opening [58].

Another possible route of transmission, which has not received much attention, is the fecal-induced aerosols by toilet flushing. Li and coworkers provided data that toilet flushing was capable to induce virus-containing aerosols reaching the toilet seat [59]. Two percent of the patients admitted to the hospital experienced diarrhea. Zheng and coworkers [60] analyzed respiratory samples, urine, feces, and serum from patients with severe disease and found that all samples were positive for virus RNA, but the longest duration was in the feces with median of 22 days.

Generally, different studies have shown the presence of SARS-CoV-2 RNA by collecting air samples and samples from fomites, but subsequent experiments to confirm the viability or infectivity are few. Santaripa and colleagues obtained air and surface samples from single rooms with SARS-CoV-2-positive patients and investigated the samples by RT-PCR. They were able to detect SARS-CoV-2 RNA. Subsequent analysis by Western blotting to find viral antigen was not possible. Propagation in Vero cells was not possible [61].

One study conducted by van Doremalen addressed this challenge using a three-jet collision nebulizer and fed into a Goldberg drum creating an aerosolized environment. They examined aerosols, plastic, stainless steel, copper, and cardboard and found that SARS-CoV-2 was viable for 3 h in aerosols. 50% tissue culture infectious dose ( $\text{TCID}_{50}$ ) was reduced from  $10^{3.5}$  to  $10^{2.7}$  per liter of air. Regarding the surfaces, the SARS-CoV-2 was viable 72 h on plastic and stainless steel. After 24 h, no viable SARS-CoV-2 was detectable on cardboard, and on copper, the SARS-CoV-2 was not detectable after 4 h [62].

Guo and coworkers investigated intensive care unit (ICU) and general ward (GW) harboring COVID-19 patients with respect to virus RNA in the air-by-air sampling, and fomites such as computer mice, trash cans, sickbed handrails, door-knobs, and floor, by swabs. Generally, virus RNA was found in the air, floor, and fomites in both departments. The positive rates were highest for ICU. Furthermore, the staff shoes were also contaminated, providing the opportunity of contact transmission. One limitation of this study was the detection of virus RNA, but not whether the virus RNA was capable of infection [63].

#### What other factors could modify the transmission?

Factors such as ozone concentration, humidity, and temperature have impact on the transmission according to Chinese studies. Yao et al. found by regression analysis that in Chinese cities during January to March 2020 the cases of COVID-19 were decreasing with higher concentration of ozone and lower humidity. In opposite, increasing temperatures seem to increase the number of cases. The authors further suggested that the indoor environment could be affected by these factors and influence the number of cases of COVID-19. In theory, it is possible in unventilated rooms that SARS-CoV-2 can be transmitted by breathing, coughing, and sneezing [64]. Generally, and in contrast, air pollution influences the susceptibility of respiratory virus infection in part by compromising the

immune system, but regarding SARS-CoV-2, pollutants such as ozone, sulfur dioxide, nitrogen dioxide, and carbon monoxide prolong the longevity of SARS-CoV-2 in the air and, in conjunction with specific climate conditions, mediated indirect transmission. It has been observed that ACE2 receptors in mice are upregulated due to pollutants [65]. The proposed “double-hit” hypothesis, chronic exposition to pollutants and SARS-CoV-2, could explain the high mortality in North Italy.

On July 9, 2020, WHO had a change in attitude that SARS-CoV-2 could be airborne-transmitted under certain circumstances such as indoor scenarios with poor ventilation. Otherwise, the airborne transmission, according to WHO, is limited to aerosol-generating procedures (AGPs) [9].

## PRECAUTIONS

Understanding the transmission routes enables the healthcare authorities to initiate precautions to protect the HCW and patients. The occurrence of SARS-CoV-2 has precipitated the lack of preparedness of the world’s healthcare systems, especially regarding the shortage of PPE. Work-related infections of healthcare workers back in 2002-2003 during the SARS-CoV-1 epidemic were reported to be 21% of the cases. The reported infection rate of COVID-19 among HCWs has shown large variation. From China, Wuhan, Wu et al. reported 3.8% infected with SARS-CoV-2, in Hong Kong the reported cases were 29%, and in the Netherlands the reported cases were 6%. One must have in mind that the numbers of SARS-CoV-2 infections also could be overestimated, if the disease was acquired in the community [57].

## ISOLATION PRECAUTIONS—SINGLE ROOM AND COHORTING

First initiative is to dilute droplets by air exchange. With increased ventilation, it is possible to reduce the concentration of droplets by 63% [66]. Another action, which very quickly can be in shortage, is single room with negative pressure. Ideally, the patient should be admitted to a single airborne precaution room with anteroom. Maintenance of negative pressure is important to prevent efflux of SARS-CoV-2 into the surrounding areas. In case, the number of patients exceeds the capacity to establish a separate ward in the hospital with cohorting staff. The medical equipment should be dedicated to the patient and disposable [33]. Chu and colleagues found by meta-analysis that wearing

face masks protected HCW (and population) against infection with SARS-CoV-2. Further protection could be achieved by using eye protection [67].

The recommendations, whether HCW should wear masks or respirators, have been conflicting. Currently, WHO, Public Health England, and Swissnosco recommend contact and droplet precaution, and the US CDC recommends airborne precautions. The European Center for Disease Prevention and Control (ECDC) and German Robert Koch institute recommend respirators for protection against airborne transmission [68].

Regarding the mask types, they have different protection efficiencies and breathability. N95 and FFP1, FFP2, and FFP3 are respirators. In Europe, FFP2 and FFP3 are available, in US N95. Other face masks are surgical masks (type II/IIR) (Fig. 1). FFP1 is the mask with the least filter capacity, since it can prevent 80% of particles greater than 0.3  $\mu\text{m}$ . FFP2 and FFP3 are 94%, respectively, and



**Figure 1.** Surgical mask used as normal equipment on a working day.

99% effective in their filter performance [68] (Fig. 2).

The purpose of surgical mask type II and type IIR is to protect the patients in the operating room from infectious secretions from HCW. Mask IIR is intended to protect HCW against splash [68]. The use of surgical mask as personal protection should be recommended [68]. Although data suggest that the ability to reduce infection rate may only be modest, which is why surgical masks should only be considered as a supplement as regards self-protection [69], Chu and colleagues' meta-analysis indicates that respirators and similar have a stronger protective effect as compared to surgical masks [67]. Putting on, wearing (donning), and upon removal (doffing) of PPE are not without risk (Video S1).

Bearded employees in the hospital sector face problems, when using masks, since the seal is not complete. Removing the beard is not an option due to personal or religious reasons. In 2015, British Health and Safety Laboratory conducted a study for the Health and Safety Executive regarding the presence of stubble and the protection. In the report, they concluded that the protection could be significantly compromised, and as the growth of facial hair continues, the protection would be further reduced [70]. To solve this challenge, the *Singh Thattha* technique has been examined in a pilot study. This technique involves the use of an elastic rubber band beard cover, that is, tied around the turban and headcloth. The technique was tested by a qualitative fit test (QFT) and a quantitative fit test (QNFT). The qualitative method is composed of sensing a test agent such as bitter or sweet. The quantitative method is based on particle counting. The study comprises in the qualitative test 27 dentists, and 25 of whom were able to detect the agents, and in the quantitative test, 5 out of 5



**Figure 2.** FFP3 mask.

passed. The limitation of the study was the small numbers of participants [71].

## DROPLET OR AIRBORNE PRECAUTION

Droplet precaution recommended by Danish authorities is based on the assumption that the transmission is—of course—by respiratory droplets. Furthermore, it implies that one should maintain a spatial distance of 1 m and wearing a mask when having contact with infected or suspected infected patient. Data from the first wave show that front-line HCWs have an increased risk of testing positive, and data also indicate that personal protective equipment may reduce that risk [72].

## AEROSOL-GENERATING PROCEDURES

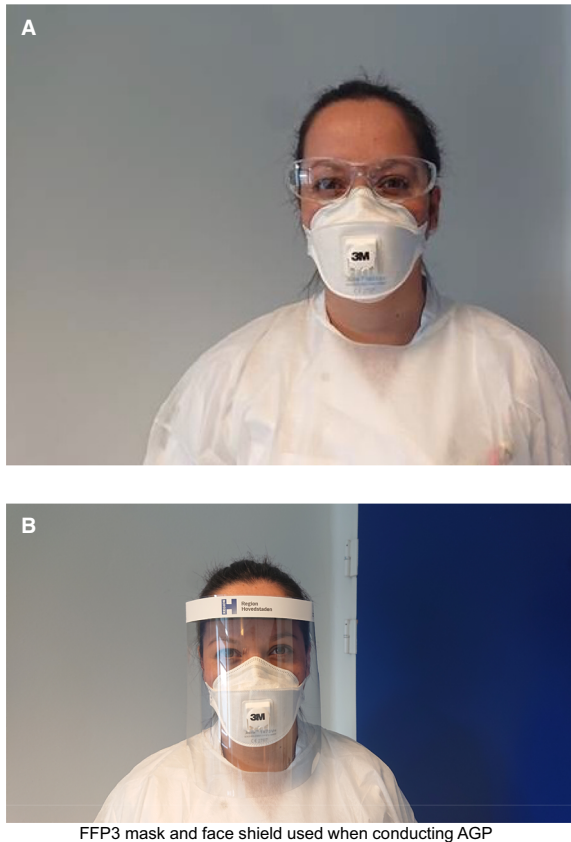
Besides aerosol formation by patients, some medical procedures generate aerosols. These procedures are characterized as high-risk exemplified by mechanical ventilation, tracheostomy, bronchoscopy, airway suctioning, turning the patient to the prone position, disconnecting the patient from the ventilator, and cardiopulmonary resuscitation [72, 73]. First, the US CDC and ECDC recommended respirators in both low- and high-risk situations. The lack of PPE made the two organizations reconsider the guidelines, so masks were protective enough in low-risk situations and respirators were reserved to high-risk situations according to US CDC. ECDC suggested that the storage of PPE should determine the use. Only when the respirators are non-accessible, the masks could be substituted [68] (Fig. 3).

## CLEANING AND DISINFECTION

Since the SARS-CoV-2 can spread to the environment due to the droplets falling down because of gravity or due to indirect transmission by patients, disinfection is essential. Disinfectants such as sodium hypochlorite are effective. Also, biocidal agents such as alcohols, hydrogen peroxide, and benzalkonium are useable. Ethanol ( $\geq 70\%$ ) reduced SARS-CoV-2 with a  $\geq 4.0 \log_{10}$  reduction. Since a toilet can act as reservoir, cleaning is important and the lid should be closed before flushing [33, 74].

Due to the initial shortage of masks in the healthcare system and the use of cloth masks in the public, the question regarding the cleaning or disinfection and reuse of the mask has been raised.





**Figure 3.** (A) FFP3 mask and goggles used when conducting AGP (B) FFP3 mask and face shield used when conducting AGP.

Disinfection of FFRs (FFP2 and FFP3) and surgical masks have been examined regarding the use of ultraviolet light (UL) dry and moist heat, and microwaves generated steam and by chemical methods in terms of alcohol, ethylene oxide, bleach, and vaporized hydrogen peroxide. UVC induces damage to the RNA and DNA. UVC is better absorbed as compared to UVA and UVB. Inactivation of SARS-COV-1 has been observed with  $\geq 4.0 \log_{10}$  reduction from FFR coupons, also in the presence of mucin. The applied UVC dose was  $1000 \text{ mJ/cm}^2$ . Examination of SARS-CoV-2 and N95 respirators has shown reduced effect using  $1980 \text{ mJ/cm}^2$  and  $3 \log_{10}$  reduction in virus titer. Despite inconsistent results, Derraik and coworkers concluded that UVC also eliminates SARS-CoV-2. Heat treatment at  $60^\circ\text{C}$  for 60 min eliminates SARS-CoV-1 and SARS-COV-2. Filtration performance can be compromised using chemical disinfection. Performance of FFRs when using UVC was not affected. The results depend on the amount of energy and number of cycles. Viability of virus would benefit from

soiled FFRs [75]. In Denmark, disinfection and reuse of masks are not recommended.

According to recommendation from the US CDC, the cloth mask should be washed daily and can dry in a warm or hot dryer. When washing the cloth, mask can be included in the regular laundry and with the use of regular detergent. It is of course important to follow the instructions from the producer. Handling the cloth mask correctly is pivotal to prevent transmission. After removal of or touching the mask, the hands should be washed or/and sanitized [76].

In 2007 in the UK, the department of health recommended that HCW should be “bare below the elbows” (BBE). The purpose was to improve the quality of the hand hygiene. Being BBE is defined as no sleeves, watches, or hand jewelry. In Denmark, being BBE also includes not wearing wedding rings, long nails, or artificial nails. The evidence to support the recommendation seems to lack. Farrington and coworkers evaluated the quality of handwashing among 88 medicals doctors and 61 medical students at a 900-bed teaching hospital in Cornwall. The participants were randomized into non-BBE and BBE, and the quality of handwashing was estimated by using fluorescent alcohol-based preparation. The authors concluded that being BBE did not significantly amend the quality of handwashing as compared to non-BBE, and especially did not improve the wrist washing. In Denmark, BBE is mandatory all thought, the evidence for reducing hospital infections is lacking, also regarding the transmission of SARS-CoV-2 [77].

## CONCLUSION

SARS-CoV-2 seems highly contagious between humans as the particle size consists of a continuum of different sizes, why the protection of health workers is important. The simplicity of droplet transmission into the dichotomy of large contra small droplets has been challenged, and influencing factors such as humidity, temperature, individual anatomic physiology, pollutants, interaction, dynamics in the multiphase gas cloud, and airflow make it difficult always to maintain this model, and may expand it to a more continuous model such as the multiphase gas cloud model. It seems possible that airborne transmission can occur in selected settings. Since the weight of evidence is growing, further investigation with modern technology and humans as objects would shed light on the transmission by droplets. At the moment, there is no clear-cut distinction between the droplet transmission and airborne transmission movement. In the

end, this is not only about protecting HCW but also about protecting the population. It seems that the Danish authorities still are in line with the WHO and in the future hopefully would be in line with Taiwan's precautionary approach.

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## CONFLICT OF INTEREST

None declared.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Video S1