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Clearing the air about airborne transmission of SARS-CoV-2

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Abstract. – The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that has created the current pandemic, has caused a worldwide worry. Different countries have since enforced varying levels of lockdowns and guidelines for their populations to follow in a serious effort to mitigate the spread. Up until recently, the majority of these regulations and policies were established on the assumption that the dominant routes of transmission of this virus are through droplets and fomite contact. However, there is now a substantial amount of research pointing towards the strong possibility that SARS-CoV-2 can spread through airborne means. The World Health Organization (WHO) and the Center for Disease Control and Prevention (CDC) have recently recognized this, which poses the question of whether our collective methods of lessening transmission risk and keeping people safe have been sufficient. This paper is a comprehensive review of the evidence on SARS-CoV-2 being an airborne disease, through different epidemiological, experimental, and animal-model based published research. Studies opposing this evidence have also been discussed. The majority of these studies are favoring the high plausibility of SARS-CoV-2 aerosol transmission, and therefore the many implications of aerosol transmission have been discussed in this paper to suggest effective mitigation and control strategies.

Key Words:
SARS-CoV-2, COVID-19, Airborne transmission, Precaution, Respiratory protection, Mask.

Introduction

As of late 2019, the Wuhan Municipal Health Commission in China mentioned an outbreak of atypical pneumonia in the city of Hubei[1]. On the 11th of February 2020, the disease caused by SARS-CoV-2 was named by the WHO as coronavirus disease 2019 (COVID-19), and by March 11th 2020, it was classified as a Pandemic with the number of cases having surpassed 100,000 internationally[1,2]. As of now, the total of cases and deaths due to COVID-19 have exceeded 204 and 4.3 million people, respectively[3].

Before 2003, human coronaviruses (CoVs) were not considered deadly. However since then, the strains Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and that of the current pandemic have evolved making CoVs much more concerning[4].

To understand the severity of such concerns, the modes of transmission of different infectious agents must be investigated to effectively mitigate their contagiousness. As this review will discuss, there has been a debate over whether SARS-CoV-2 spreads by droplets and fomite contact, or through airborne routes. Here we attempt to give a general background on what airborne transmission entails, lay out the published evidence with and against airborne transmission, and the implications of spreading through airborne routes.

SARS-CoV-2 Transmission Dynamics

The Incubation Period

An early study where 88 confirmed cases were evaluated using travel history and onset of symptoms showed a mean incubation period of 6.4 days[5]. Another study[6] found the mean incubation

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period to be 5.2 days. A few cases in which symptoms onset took 19 days were reported[7]. However, due to the rarity of it taking that long, and based on other studies, experts maintained a 10-14 days' quarantine period in case of contact with a positive COVID-19 case[8,9].

The Basic Reproductive Number (R0)

The basic reproductive number (R0) is arguably the most important parameter in determining transmissibility[9]. Several published studies[9-12] have attempted to estimate R0 but had a low level of accordance. This estimation is model-based and depends on varying biological, environmental, and socio-behavioral factors that must be deduced with caution[10]. This number also depends on control factors including the initial number of cases in an outbreak, not isolating upon the onset of symptoms, whether all contacts are traced, transmissions that had occurred before symptoms onset, and lastly, subclinical infections that are not caught[9,10]. Initially, WHO estimated it to be between 1.4 and 2.5 for SARS-CoV-2[11], however, most studies have predicted R0 to be within the range of 2.24 and 3.58[12].

The debate on the Modes of Transmission of SARS-CoV-2

SARS-CoV-2 is thought to transmit via the dispersion of droplets from an infected person and direct or indirect contact with fomites. There have also been instances where airborne transmission was suspected[13,14].

Since the beginning of the pandemic, the WHO and the CDC advocated for protective measures such as quarantine, keeping a physical distance between people, wearing masks, continuous sanitization of spaces, and handwashing. All of these precautions focus on stopping transmission through droplet and contact routes[15,16].

Since then, there have been many experiments and studies suggesting that the airborne, or aerosol transmission of SARS-CoV-2, is a viable route that needs more attention. For example, in contact tracing experiments including a restaurant in China and a choir practice in Washington DC, it was shown that people seated at a distance of more than 6 feet from the infected person were infected with COVID-19. This implies that the virus spreads through the air[17,18].

It seems that in China, they acknowledged the possibility of airborne transmission of SARS-CoV-2, since "aerosol transmission" was added to China's latest National Health Commission's (NHC) diagnosis and treatment plan[19,20].

The WHO changed its terminology in July 2020, to acknowledge this reality saying, "short-range aerosol transmission, particularly in specific indoor locations, such as crowded and inadequately ventilated spaces over a prolonged period of time with infected persons cannot be ruled out"[21]. The CDC then amended its guidelines on the 5th of October, 2020, to state the following: "There are several well-documented examples in which SARS-CoV-2 appears to have been transmitted over long distances or times. These transmission events appear uncommon and have typically involved the presence of an infectious person producing respiratory droplets for an extended time (>30 minutes to multiple hours) in an enclosed space. Enough virus was present in the space to cause infections in people who were more than six feet away or who passed through that space soon after the infectious person had left"[22]. In the same document, however, they mentioned that the epidemiology of SARS-CoV-2 shows that close contact, hence droplets, was still the main driver behind transmission[22]. Recently, in April 2021 and May 2021, the WHO and CDC respectively updated the information on their websites stating that infection could occur due to the inhalation of aerosols or small particles containing SARS-CoV-2[22,23]. The WHO is now emphasizing the importance and urgent need for more high-quality research to clarify the different routes of transmission[21]. This is especially important in order to be able to prevent transmission more efficiently.

Features of Airborne Transmission

The Difference Between Droplets and Aerosols

The classification system for respiratory disease routing, which is based on large and small droplet transmission was first reported by Wells[24] in the 1930s on tuberculosis transmission. Aerosols are referred to as particles or poly-dispersed droplets that evaporate into "droplet nuclei"[19,25]. They can be retained in the air for long periods, which means that humans are more susceptible to inhaling them, especially since they can travel for significant distances[25]. The distance traveled depends on air currents and the ventilation of a specific area[19].

WHO suggests that those particles smaller than 5 μm are defined as aerosols and bigger ones as droplets[26]. Bigger particles are believed to settle more quickly, hence, do not pose the same dangers as aerosols. They are most likely to fall to the ground at a faster rate and can also end up as fomites[27,28].

Aerosol Generation

The volume and size of droplets or aerosols that a person expels can depend on the activity they participate in[29]. Coughing and sneezing tend to release bigger droplets, though, these can also atomize into smaller aerosols[13,29]. Larger droplets also tend to occur from the laryngeal, oral or nasal cavities[29,31]. Smaller aerosolized droplets, on the other hand, tend to be released from the bronchioles of the lungs, in the lower respiratory tract[32,33]. This means that regular breathing, physical activities that increase the exhalation rate, and even speaking loudly or singing can give rise to smaller particles[34-37].

It has also been suggested that pathogen-loaded particles can be re-suspended into the air when enough force is applied to different surfaces such as the floor. For example, while walking, particles that had previously landed on the floor can rebound to higher levels and become aerosolized[38].

Aerosol generating procedures (AGPs) in medical settings can also give rise to aerosols, such as in dental procedures or those procedures involved with the respiratory tract[39-41]. For example, intubations and extubations[39]. There has also been some recent evidence of aerosolization in the toilets from flushing, where SARS-CoV-2 was found in feces[42,43].

Mechanisms of Particle Deposition in the Respiratory Tract

The risk of infection for a susceptible host depends on the amount of viable pathogen in the inhaled aerosol or droplet, and the site it is deposited[44]. The nose is much more efficient at filtering larger inhaled particles; however, the oropharynx is not as efficient and there is a higher possibility that smaller particles penetrate the lower respiratory tract[45,46]. It is also suggested that droplets bigger than 20 μm cannot deposit in the lower respiratory tract[47].

Some very important determinants of the deposition rate of particles onto the airway surfaces are their mass, diameter, and shapes[44]. The inspiratory flow a person portrays can also have an effect. Slow and deep inspirations favor deeper penetration of the particles in the lungs, while faster inspirations are more likely to cause deposition of particles in the tracheobronchial region[45,46].

Moreover, it has been shown that the angiotensin-converting enzyme 2 (ACE2) receptor is what initiates the intake of SARS-CoV-2 in the respiratory track cells[14]. The virus links to this receptor on the membranes of the cell and allows entry into the host cells[14,48,49]. The ACE2 receptor is found in the cells of various organs, which is a cause of concern on whether SARS-CoV-2 can infect more than just the respiratory tract[14].

Airborne Transmission of SARS-CoV-2: Available evidence

As previously mentioned, there has been an ongoing dispute concerning the spread of the SARS-CoV-2 virus via aerosols, predominantly where large droplets and direct physical contact modes of transmission were absent. The controversy arose over whether the small aerosols could be a major route of transmission of the virus, thus a plethora of research was carried out investigating and discussing this plausibility. In this section, we summarize the outcomes of the studies from the beginning of the COVID-19 pandemic until March 2021 (Table I).

Evidence of SARS-CoV-2 Airborne Transmission

Initially, scientists reported that most SARS-CoV-2 infections spread through close contact with an infected person. However, under certain circumstances, airborne transmission may occur[50,51]. Asadi et al[52] argued that there is a considerable probability that speaking gives rise to aerosolized SARS-CoV-2 particles, an under-recognized, yet important mechanism . Banik and Ulrich[53] suggested that suspecting the possibility of aerosols transmission of SARS-CoV-2 is reasonable, as it shares important characteristics with other respiratory viruses known to spread mainly via short-range aerosols. Such viruses include SARS, MERS, influenza A, and other seasonal coronaviruses (CoVs)[53]. Gralton et al[54] collected droplets and aerosols from the breaths and coughs of symptomatic patients with respiratory infection symptoms and tested them for the presence of several viruses using reverse transcription-polymerase chain reaction (RT-PCR). The results revealed that the RNA of the respiratory syncytial virus and influenza A virus were detected in the large droplets of 8% and 3% of the samples respectively. In addition, the RNA of parainfluenza virus and human rhinovirus was detected in both large droplets and small-sized aerosols as well. This study demonstrated the

Table I. Epidemiological and experimental investigations on the possibility of airborne transmission of SARS-CoV-2, up to March 2021.

Type of evidence	Testing Location	Main observations and findings	Ref.
Supporting evidence	Choir, USA	Out of 61 attendees at a 2.5 hours choir rehearsal at Skagit Valley Chorale of Mount Vernon, 53 were infected and two died. This was despite all attendees being asymptomatic, and all precautionary measures against droplet and fomite transmission being adequate.	17
	Restaurant, China	In an air-conditioned restaurant, ten persons from 3 families were found to be infected among the diners, despite no observed close contact, and a distance > 1 m between them.	18
	Bus, China	Among the 68 passengers of the first bus, which carried an infected person, 24 were infected. This came with a 41.5-fold higher risk of infection than the other bus, which had no infected person. The buses were equipped with air recirculation systems, and close contact among the riders was not observed.	69
	Shopping mall, China	Direct and indirect tracing on different floors of the mall showed no close contact among staff and customers, although some tested positive for COVID-19, which suggests the possibility of airborne transmission of the virus.	70
	Fitness dance classes, South Korea	The transmission of the virus from the instructors to the students was mostly recorded in the crowded and small-spaced classes, where intense physical activities were carried out.	71
	Quarantine hotel, New Zealand	New positive cases were detected, although person-to-person contact or fomite route of transmission was unlikely, suggesting airborne transmission had taken place in the unventilated corridors of the hotel.	73
	Lab, USA	The virion size and general appearance of aerosolized SARS-CoV-2 were similar to that before aerosolization, and the virus remained infective for up to 16 hours.	82
	Hospital, Singapore	Air samples from two out of three AIIR rooms were positive for SARS-CoV-2 RNA. The diameter of the tested aerosol particles ranged between 1-4 µm and > 4 µm.	83
	Hospital, London	Air samples from several clinical and public areas of the hospital were tested, and 38.7% of them tested positive for the viral RNA, suggesting the possibility of airborne transmission of SARS-CoV-2.	84
	Hospital, China	Air samples taken from the ICU and the general ward of the hospital showed that 35% and 12.5% of them were positive for the virus, respectively. The virus was suspected to have been able to transfer through the air for up to a distance of 4 meters.	85
	Hospital, Italy	SARS-CoV-2 RNA was detected in all air samples from the contaminated areas (ICU and corridors of patients' wards).	87
	Hospital, China	Air samples taken from the vicinity of 35 COVID-19 patients showed detection of the virus in 3.8% of them. This indicated the direct release of the virus into the environment via breathing, with a breath emission rate of 103-105 RNA copies/min.	88
	Hospital, USA	Air samples taken from isolation rooms and hallways showed that 63.2% and 58.3% of them were positive for viral RNA, respectively. Cell culturing showed evidence of virus replication (viability) in some samples.	89
	Hospital, USA	Viable viruses were detected in air samples from areas about 2-4.8 m away from the patients, with 6-74 TCID50 /L of air.	90
	Lab, USA	The stability of SARS-CoV-2 was studied. Per liter of air, a reduction of viral titer from 103.5 to 102.7 of the 50% TCID50 was observed, however, the virus remained infective for up to 3 hours.	91
	Car, USA	Viable viruses were detected in air samples collected from a car driven by a mildly symptomatic COVID-19 patient. Aerosol samples ranging from 0.25 to 5 µm in size.	92
	Lab, UK	Under four experimental conditions (artificial saliva, medium and high relative humidity, and in the dark), SARS-CoV-2 was stable and remained infectious for up to 90 minutes.	93
	Hospital, Kuwait	From the size-fractionated air samples, 6% were positive for viral RNA, with concentrations of 3-25 copies/m3. Different sizes of airborne particles were found at different sampling locations, suggesting that the size of the airborne particles depends on several environmental factors.	94
	Hospital, Sweden	Out of 19 samples of the COVID-19 wards' room vents, 7 samples of the viral N gene and 4 samples of the E gene tested positive. In addition, the central ventilation HEPA exhaust filters of the COVID-19 ward and the adjacent wards at over 50 m away also tested positive for the viral RNA, indicating that long-distance transmission of the virus is possible.	96

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Type of evidence	Testing Location	Main observations and findings	Ref.
	Lab, France	A simple quantitative model to study the flow rate of inhaled aerosols showed that in most cases, the risk of contamination with the virus in outdoor areas is much lower than indoor areas, even in crowded locations.	99
	Hospital, USA	Portable dehumidifiers were distributed at selected locations in a hospital ward and used to collect air samples with aerosolized SARS-CoV-2 in the condensates. Analyzing the samples for both viral capsid protein and nucleic acids showed positive results for the viral antigens, while the viral RNA was not detected.	100
	Hospital, China	Among the different areas tested in a hospital, patients' toilets showed the highest detection of SARS-CoV-2 RNA.	101
	Hospitals, China	SARS-CoV-2 RNA with a concentration of 19 copies/m3 was detected in the air samples from the patients' toilets. In addition to traces found in the isolation rooms and patients' wards.	102
	China	A significant association between the daily-confirmed cases and PM pollution was found in 63 cities.	110
	Bergamo area, Italy	The detection of SARS-CoV-2 E and RdRp genes were found in association with PM10, indicating the possibility of PM to carry viruses.	111
	Hospital, Malaysia	SARS-CoV-2 was detected in indoor PM.2.5, suspecting that patients could shed these ambient particles, which then recirculate in the air.	112
	USA	Ecological regression analysis showed a positive association between higher PM2.5 exposure and the increased COVID-19 cases as well as mortality rates.	113
	UK	There is a correlation between PM2.5 and the number of COVID-19 cases, as 1 m 3 of PM2.5 on average was linked to a 12% increase in COVID-19 cases.	114
	Lab, South Korea	Naïve ferrets that had indirect contact with infected ones through a permeable partition were positive for viral RNA, suggesting airborne transmission of the virus.	117
	Lab, Netherlands	In an experimental setup, naïve ferrets were kept more than one meter away from the infected ones with an air connection between them. Infection among the naïve ones was detected, indicating the possibility of the virus to remain viable while it is airborne for such distance.	118
	Lab, Hong Kong	An extra layer of surgical masks was used to separate naïve Syrian hamsters from infected ones. Of the naïve hamsters, 12.5% were tested positive for the viral RNA, whereas 60% of the hamsters without an extra surgical mask layer were infected.	119
	Lab, USA	Syrian hamsters infected with SARS-CoV-2 via aerosols showed a higher viral load in the respiratory system in comparison to those infected via the intranasal route. No virus was detected in those infected by the fomite route of transmission.	120
	Lab, Hong Kong	Among golden Syrian hamsters, transmission of SARS-CoV-2 was more efficient through aerosols and direct contact than via fomites.	121
	Lab, China	Human ACE2 transgenic mice were infected via the intranasal route using bio-aerosols, and the virus was detectable after 25 minutes of exposure with a mean load of 102.07 viral RNA copies/ml.	122
Non-supporting evidence	Hospital, China	SARS-CoV-2 viral RNA was not detected in any of the tested air samples in the AIIRs, suggesting that airborne transmission might not be the main route of transmission.	123
	Hospital, Hong Kong	Nosocomial transmission of SARS-CoV-2 was traced among healthcare workers who cared for COVID-19 patients. None of the quarantined healthcare workers were infected, and samples taken from areas 10 cm away from the patients' chins were also negative for the virus.	124
	Hospital, China	Out of 135 tested air samples, none were positive for SARS-CoV-2 RNA, suggesting that strict implementation of disinfection procedures and improved room ventilation could lower the risk of airborne transmission.	125
	Hospital, Hong Kong	Among the healthcare workers and other patients who were in close contact with a COVID-19 patient, none tested positive for the virus, suggesting that airborne transmission is not the main route of SARS-CoV-2 transmission.	127
	Hospital, Iran	Ten air samples taken about 2-5 m away from COVID-19 patients' beds were tested and all were negative for viral RNA.	128
	Hospital, China	All of the 44 collected air samples were tested negative for SARS-CoV-2.	129

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Type of evidence	Testing Location	Main observations and findings	Ref.
	Households, Germany	Air samples were collected from poorly ventilated rooms in households, where at least one positive COVID-19 family member was quarantined without isolation from other family members. All of the air samples tested negative for the virus.	130
	Lab, Netherlands	The dynamics of exhaled respiratory droplets were analyzed and modeled, and their size distribution, total numbers, and volumes were measured. The study concluded that SARS-CoV-2 aerosol transmission might be possible, but not in an efficient manner.	131
	Lab, USA	The effect of simulated sunlight, relative humidity, and suspension matrix on the stability of aerosolized SARS-CoV-2 was examined. The decay rate of the virus was significantly affected by simulated sunlight and matrix, as 90% of the virus was inactivated in less than 20 minutes. This suggests that environmental conditions may play a role in the potential of airborne transmission of the virus.	160
	Lab, Cyprus	Fluid dynamic models were developed and implemented to study the effect of different weather conditions on the airborne transmission of SARS-CoV-2. This showed that the viability and infectivity of the virus dropped significantly at low relative humidity and high temperature, although it could remain viable at high relative humidity and any temperature if it had high concentrations.	161

possibility of viral spread through aerosols generated by breathing and coughing[54]. Milton et al[55] collected droplet particles exhaled by seasonal influenza patients and used quantitative RT-PCR to detect the viral RNA. They found that the viral RNA was identified in 78% of the aerosols samples from patients wearing face masks. The viral RNA copy number in those samples was 8.8 times higher than that found in larger droplets. Furthermore, the infectious virus particles were successfully recovered by cell culturing from two aerosol samples, which had the highest copy numbers of viral RNA[55]. As can be seen, the debate on the possibility of aerosol transmission is not restricted to SARS-CoV-2. Similar discussions were made on the transmission modes of the influenza virus. A considerable number of studies[56-66] provided supportive evidence for influenza virus transmission via aerosols, such as experimental investigations, epidemiological studies, testing of simulation models, generation and testing of artificial aerosol, and the detection of viable viruses in aerosols. Compared to other pathogens and even other modes of transmission, there is more epidemiological and experimental evidence that SARS-CoV-2 could be airborne[67], whereas such evidence is not available for other routes of transmission such as via contact and large droplet[19]. Additionally, the infectious agents of some diseases such as measles and tuberculosis were not recovered in cell culture from air samples, however, they are still considered to be airborne[68].

Evidence from Epidemiological Investigations Supporting Airborne Transmission of SARS-CoV-2

Several epidemiological studies speculate that certain COVID-19 outbreaks have occurred due to aerosol transmission. One specific outbreak of COVID-19 was discovered in a restaurant in Guangzhou, China, which was air-conditioned. The key factor for infection was suspected to be the airflow direction carrying aerosolized droplets from an asymptomatic patient, as the distance between other diners was >1 m and no close contact between them was observed[18]. Miller et al[17] studied an outbreak that had occurred at Skagit Valley Chorale of Mount Vernon, Washington, USA. Out of 61 attendees during a 2.5 hours' choir rehearsal, 53 were infected and two died. They noted that aerosol transmission was more likely to be the culprit than large droplet and fomite transmission, as taken precautions were adequate for droplet and fomite transmission and all attendees were asymptomatic. In addition, the dense occupancy and loud vocalization, coupled with the long duration of attendance and poor ventilation, may have increased the risk of aerosol transmission of the virus[17]. A study by Asadi et al[35] showed that there is a positive correlation between the rate of particles emitted during speech and the loudness of vocalization, in which about one to 50 particles could be emitted per second. Compared to breathing, speech can produce larger particles with greater amounts, therefore, it is of higher concern when considering the transmission of pathogens[35]. In a cohort study of a community outbreak of COVID-19 in Zhejiang province, China, the potential of SARS-CoV-2 airborne transmission among the riders of two separate buses was investigated. This study showed that in the first bus, which was carrying the infected patient, 35.3% of the passengers tested positive for COVID-19. However, in the other bus, none of the passengers were infected. Furthermore, the risk of infection in this bus was 41.5 times lower than the first bus. These results suggest that there is a potential for airborne transmission of the virus specifically in enclosed environments where the air is recirculated[69]. Upon investigation of a cluster of COVID-19 cases at a shopping mall in Wenzhou, China, Cai et al[70] traced the direct and indirect contacts of the staff and customers at different floors of the mall. They found that some of the positive cases had no close contact with the index patient or with any of the other positive cases. Thus, they suggested that aerosol transmission could be one of the possible indirect modes of transmission among the individuals present at different levels of the mall[70]. In South Korea, a cluster of SARS-CoV-2 infection among attendees of fitness dance classes in a group of sports facilities was investigated. The transmission of the virus was found to occur from the instructors to the students during the fitness classes, and then to their families and coworkers. The study showed that most of the cases were reported in small spaced and crowded classes, specifically in those where people were undergoing intense physical activities. In these classes, turbulent airflow could be generated, which in turn could have led to denser transmission of virus-laden aerosols and droplets especially in the presence of moist and warm environments. In comparison, there was no infection detected in the yoga and Pilates classes[71]. In Hong Kong, contact-tracing data showed that five to seven super spreader events were believed to have led to 80% of the local transmission in the country. Since the recommended and followed guidelines for the prevention of SARS-CoV-2 heavily relies on droplet and fomite modes of transmission, it begs to question whether airborne transmission could be considered a viable mode, yet a neglected one[72]. Likewise, there was an outbreak of COVID-19 in a managed isolation and quarantine hotel in New Zealand. Here, direct person-to-person contact was not observed, and the fomite route of transmission was considered unlikely. This gave rise to the speculation that transmission may have occurred via aerosol particles, especially that there was no ventilation in the corridors of the hotel[73].

Evidence from Experimental Investigations Supporting Airborne Transmission of SARS-CoV-2

Several experimental investigations have revealed the prospect of airborne transmission of SARS-CoV-2[72,74-81]. A recent study[82] showed that the virus retained its integrity and infectivity, including size and morphology, for up to 16 hours in experimentally generated aerosols. The aerosolized virions were similar to those examined in samples before aerosolization[82]. Another study conducted by Chia et al[83] showed that 66.7% of air samples from airborne infection isolation rooms (AIIR) tested positive for SARS-CoV-2. This was found in particles of sizes > 4 µm and 1 to 4 µm and with RNA concentrations within a range of 1.84×10^3 to 3.38×10^3 copies per m^3 of sampled air[83]. A similar study in London[84] revealed the detection of SARS-CoV-2 RNA in 38.7% of air samples in several clinical and public areas of a hospital during the peak of the COVID-19 pandemic. In this study, Zhou et al[84] suggested that the presence of infectious viral particles is possible, yet no virus was cultured, as the cycle threshold (Ct) value of the RT-PCR test was > 30. They believed that the viral RNA might have been deposited more than 2 hours before sampling and detection. This lead to the elucidation that the length of time of virus deposition, in addition to low viral RNA levels, could have resulted in the unsuccessful culturing of the virus[84]. Air samples were collected and tested by Guo et al[85] from an intensive care unit (ICU) and a general ward for COVID-19 in a hospital in China. They detected SARS-CoV-2 RNA in 35% and 12.5% of the air samples respectively and suspected that the aerosols could transfer for up to 4 meters[85]. In addition, another study conducted by Wofel et al[86] found that the average viral load in oral fluid aerosols was 7×10^6 copies per ml, suggesting a 0.37% probability that a 10 µm droplet aerosol would contain at least one virus[86].

Moreover a study in Milan, Italy, evaluated the air and surface samples in COVID-19 wards of a hospital and found that all air samples from the patients' area and the ICU area were positive for viral RNA[87]. Another study in China[88] recruited 35 COVID-19 patients to test their exhaled breath condensate, and air and swab samples for the presence of SARS-CoV-2 RNA. Subsequently, it was shown that 3.8% of the air samples tested positive for the viral RNA, indicating the contamination of the air in the hospitals that had COVID-19 patients. The study also reported the direct release of SARS-CoV-2 into the air via breathing and estimated that the breath emission rate of the virus could be about 10^3-10^5 copies of RNA per minute[88]. A study[89] performed in Nebraska Medical Center, USA, showed the presence of SARS-CoV-2 viral RNA in all of the tested air samples from the quarantine and isolation centers. In addition, cell culturing showed viable viruses in two of the samples, indicating the likelihood of spreading the infectious virions in aerosols. Although the size range of the droplets was not determined, the study[89] proposed that aerosols carrying the virus could be generated by the SARS-CoV-2 infected individuals even without coughing[89]. In another study conducted by Ledincky et al[90], viable virions were isolated from air samples collected in a hospital room of two COVID-19 patients. The samples were collected from areas about 2 to 4.8 meters away from the patients, and the results showed the presence of the virus with concentrations of 6 to 74 of median tissue culture infectious dose ($TCID_{50}$) units per liter of air[90]. Upon studying the stability of SARS-CoV-2 and its decay rate, it was estimated that the viral matter was capable of remaining viable for up to 3 hours, corroborating that aerosol transmission is plausible[91]. In another study, Ledincky et al[92] collected air samples from a car driven by a COVID-19 patient, and viable viruses were detected in the airborne particles with sizes ranging from 0.25 µm to 0.5 µm[92]. Another study[93] also found that SARS-CoV-2 was stable in artificial saliva under different experimental conditions and remained viable for up to 90 minutes. In a recent study in Kuwait[94], size-fractionated air samples from a hospital were collected and analyzed for the detection of airborne SARS-CoV-2 RNA. The study showed that 6% of the air samples tested positive for the viral RNA, with a concentration range of 3 to 25 copies/m^3. There were different sizes of airborne particles depending on the location of the sampling, which suggests that there are several factors at play when it comes to the size range of the virus-laden particles. Symptomatic patients' rooms contained large virus-laden particles (> 10 µm), the rooms of the intubated patients had fine virus-laden particles (< 2.5 µm), while the coarse virus-laden particles (2.5-10 µm) were detected in all tested locations[94].

Evidence of Airborne Transmission of SARS-CoV-2 in Poorly Ventilated Environments

The airborne transmission of SARS-CoV-2 in poorly ventilated environments is of even higher concern. Heating, Ventilation and Air Conditioning (HVAC) systems play a key role as a primary measure for disease control, specifically in confined spaces where the air is recirculated. Correia et al[95] hypothesized that improper use of HVAC systems could contribute to the spreading of the virus-laden aerosols. This was particularly hypothesized to be true if the air was recirculated in confined compartments with infected individuals, the ventilation system was shared in a multiple floored building, or if the exhaust filtering systems were inadequate[95]. In a hospital in Sweden, air samples from the room vents in COVID-19 wards were tested for the N and E genes of SARS-CoV-2. From the 19 samples taken from the room vents, the N and E genes were found seven and four times respectively. The central ventilation high efficiency particulate air (HEPA) exhaust filters tested positive for both of the genes as well. Furthermore, the viral genes were detected in exhaust filters of adjacent wards located over 50 meters away from the patient areas, indicating the possibility of long-distance transport of the virus through air ventilation ducts[96]. Despite the virus not being cultured, the researchers still suggested that the virus may have still been viable and airborne transmission is probable, specifically in closer distances to the infected patients and at the peak of their contagiousness[96]. Stadnytskyi et al[97] revealed that thousands of small-sized oral fluid droplets could be emitted per second during loud speech in confined spaces, which could reach the lower respiratory tract and cause infection[97]. In another study by Somsen et al[98], it was proposed that even low initial concentrations of virion-laden particles could remain infectious over long periods of time, despite environmental factors such as temperature and humidity and especially in poorly ventilated spaces[98]. A study used quantitative models to show that the outdoor risk of aerosol contamination is usually lower than indoor risk by order of magnitude. Several climate and meteorological factors play a role in the outdoor risk of contamination, specifically temperature, wind, and relative humidity. Additionally, certain parameters should be found outdoors in order to be comparable to indoor conditions in terms of aerosols stability and airborne transmission of the virus[99]. In another study[100] carried out in a hospital ward located at the University of Maryland Medical Center, Baltimore, MD, USA, portable dehumidifiers were used to collect air samples, which could carry virus-laden aerosols in the condensates. They detected the viral spike protein at a concentration of 2.61 ng/ml. The viral RNA was not detected, which might have been due to the destabilization of the low viral RNA load in the chambers of the dehumidifiers[100].

Evidence of Airborne Transmission of SARS-CoV-2 Via Fecal-Derived Aerosols

Transmission of the virus via fecal aerosols might be possible by the improper use of toilets. Ding et al[101] tested air and surface samples from toilet and non-toilet environments in a hospital and found that most of the detected SARS-CoV-2 aerosols were those from the patients' toilets[101]. A study was conducted in Wuhan, China[102], in which aerosolized viral RNA was measured in two hospitals. Trace amounts (19 copies/m^3) were found in the air samples from the mobile toilet rooms used by the patients; an area where the detected viral load was higher compared to other tested locations, such as the ventilated patients' rooms and isolation wards[102]. Another study[103] used fluid dynamic simulation models to estimate the fluid flow characteristics and the generation and movement of the droplets during toilet flushing. It was found that about 40-60% of the total number of aerosol particles could transport toilet seat upward, promoting the spread of the virus on a large scale[103].

Particulate Matter Air Pollution and its Contribution to SARS-CoV-2 Airborne Transmission

Air pollution with particulate matter (PM) has been considered an important contributor to the spread of airborne pathogens[104]. Certain natural and human-induced activities result in a mixture of solid airborne particles such as dust, fibers, organic combustion particles, microplastics, industrial emissions, etc. Viruses could be clustered, preserved, and remain stable for a long time when held to the PM pollutants, and could be carried over long distances in the air. The small size virus-laden PM (< 5 µm) could easily reach the lower respiratory tract and sediment in the bronchi and the alveoli of the lungs upon inhalation[104,105].

Several studies[106-109] showed a considerable link between PM air pollution and the spread of SARS-CoV-2, which indicated the possibility that PM could carry SARS-CoV-2 virions in the air. For instance, in a study conducted in China[110], a significant positive association between the daily confirmed cases of COVID-19 and PM pollution was found in 63 cities. A higher overall effect of PM of an aerodynamic diameter of < 2.5 µm ($PM_{2.5}$) was observed, comparable to those of aerodynamic diameters of 10 µm (PM_{10})[110]. In Italy, Setti et al[111] tested airborne PM_{10} samples from an industrial site for the presence of SARS-CoV-2 RNA. They found that 15 samples and four samples tested positive for the E gene and RNA-dependent-RNA-polymerase (RdRp) gene respectively. This suggested that PM_{10} could be a carrier for the virus in the air[111]. In another recent study[112], indoor $PM_{2.5}$ was sampled from a hospital ward in Malaysia, and SARS-CoV-2 RNA was successfully detected in the samples of the ambient particles. It was suspected that the virus-laden $PM_{2.5}$ was shed from the patients in the wards and circulated in the air. Additionally, the physical activities and movements of the health care workers and the patients in the enclosed rooms could have contributed to the increase of the PM concentrations[112]. In the United States, performing an ecological regression analysis showed a positive association between higher historical $PM_{2.5}$ exposure and an increase of COVID-19 infectivity and mortality rates[113]. Similarly in England, a study showed that there was a high correlation between $PM_{2.5}$ and the number of COVID-19 cases at different locations. The results showed an increase of 1 m^3 of $PM_{2.5}$ long-term average to be linked to a 12% increase in COVID-19 cases[114].

Evidence from Animal Models Supporting Airborne Transmission of SARS-CoV-2

The use of animal models in research investigations is important to understand the pathogenic mechanisms and transmission of a disease, test treatments, and develop effective therapeutic strategies[115,116]. Several studies[117-122] showed the use of different representative animal models to demonstrate the possibility of airborne transmission of SARS-CoV-2. In one study[117], ferrets were used to investigate the transmission mode of the virus. The naïve ferrets had indirect contact with the infected ones, as they were separated by a permeable partition. Despite that, they tested positive for the viral RNA[117]. In another study[118], naïve ferrets were kept one meter away from the infected animals and they tested positive for viral RNA on their third day of exposure. Syrian hamsters were also used as animal models for the investigations of SARS-CoV-2 transmission and showed more efficient transmission via aerosols than fomites. Chan et al[119] used an extra layer of surgical masks to separate the naïve Syrian hamsters from the infected ones. After four days of exposure, 12.5% of the naïve hamsters tested positive for the viral RNA, and 60% of those without the surgical mask layer were infected and developed the clinical signs[119].

In another preprint study, Port et al[120] inoculated SARS-CoV-2 in two groups of Syrian hamsters. One via the intranasal route and the other via aerosols. One day post-inoculation, they detected the virus in all of the aerosol-infected hamsters, and the viral load in the trachea and lungs was found to be higher than in those infected via the intranasal route. On the other hand, the virus was not detected in the animals exposed to fomites after similar exposure time, suggesting a higher efficacy of airborne transmission compared to that of fomites[120]. Sia et al[121] used golden Syrian hamsters to study the pathogenesis and transmission of SARS-CoV-2 and suggested that the virus was transmitted mainly and more efficiently via aerosols in comparison to fomites. This came as all of the experimental animals were tested positive for the virus from their nasal wash samples[121]. Transgenic mice were also another choice of animal models for such investigations. Bao et al[122] inoculated human ACE2 mice with the virus via the intranasal route using bio-aerosols. The results showed detection of the virus after 25 minutes of exposure with a mean viral load of $10^{2.07}$ RNA copies/ml[122].

Evidence Against Airborne Transmission of SARS-CoV-2

Epidemiologic and Experimental Investigations Against Aerosol Transmission of SARS-CoV-2

Alternatively, several studies[123-126] were unsuccessful in detecting SARS-CoV-2 viral RNA in air samples of clinical wards. In an epidemiological investigation in Hong Kong[124], 42 confirmed cases were studied for the possibility of nosocomial transmission among healthcare workers who cared for Covid-19 patients. Eleven of the healthcare workers were quarantined for 2 weeks but none of them were infected. Besides, SARS-CoV-2 was not detected in any of the eight samples taken at a 10 cm distance from the patients' chin[124]. Similarly, an outbreak investigation in Hong Kong was reported and included a patient who was in close contact with other patients and healthcare workers in a general ward, before being diagnosed as a COVID-19 patient. After contact tracing, a total of 71 staff and 49 patients were found, from which 30 staff and 22 patients had developed fever and respiratory symptoms throughout the 28 days of surveillance. However, none of them tested positive for SARS-CoV-2. Based on those observations, the study suggested that the airborne route is not the main route for SARS-CoV-2 transmission. Furthermore, they believed that basic control measures, such as wearing surgical masks and routine hygiene procedures can control the spread of the virus and prevent the risk of nosocomial transmission[127]. Faridi et al[128] investigated ten air samples from COVID-19 patient's wards in the largest hospital in Iran. The samples were collected about 2-5 m away from the patients' beds. Their study showed negative results for SARS-CoV-2 RNA in all of the tested air samples[128]. Moreover in a similar study[129], none of the 44 air samples collected from a hospital in Wuhan, China, were positive for SARS-CoV-2 RNA. Cheng et al[123] indicated that aerosols transmission is not the predominant route, as the virus was not detected in any of the tested air samples obtained from six AIIRs, each with one COVID-19 patient and with a ventilation system of 12 air changes per hour[123]. Li et al[125] tested 135 aerosol samples from 45 locations of a hospital where severe COVID-19 patients were treated, and all were negative for the viral RNA. They advocated that the likelihood of SARS-CoV-2 aerosol transmission would be low due to the implementation of strict disinfection procedures and the maintenance of proper room ventilation systems[125]. Liu et al[102] detected low concentrations of aerosolized SARS-CoV-2 in patients' wards and isolation rooms. It was suspected that the proper ventilation procedures at those facilities were at play[102]. A preprint study in Germany analyzed 15 air samples obtained from poorly ventilated rooms in households under quarantine conditions, with at least one COVID-19 patient living under one roof with their family members. This study failed to detect SARS-CoV-2 RNA in all of the tested air samples and proposed that aerosol transmission would play a minor role compared to transmission through droplets[130]. Another study[83] found two-thirds of the tested air samples from the AIIRs to be positive for the viral RNA. However, they still suggested that the current evidence for the airborne transmission of

SARS-CoV-2 does not seem enough. More enhanced experiments on virus culture are required to determine the viability of the virus and confirm the true potential of airborne transmission[83]. In another recent study, Smith et al[131] considered the aerosol transmission of SARS-CoV-2 in confined spaces using a dynamic model. They also suggested that airborne transmission of the virus is possible but inefficient, especially from asymptomatic or mildly symptomatic patients whose saliva would generally contain lower viral loads[131]. Klompas et al[27] implied that generating aerosols from speaking and coughing or the possibility of recovering viral RNA from the air are not enough proof for airborne transmission of the virus. This was because some other factors play a role in infection, such as the route and duration of exposure, inoculum size, and host defenses[27]. Furthermore, health officials indicate that there is inadequate evidence to prove airborne transmission of the virus[21,132]. The WHO specified that the evidence available to us does not validate or reflect normal human conditions, confirm the presence of viable viruses, or confirm the possibility of other modes of transmission such as droplet or fomite routes[21]. Some of the limiting factors in providing evidence of airborne transmission include the difficulty of direct detection or culturing of viable viruses from the air, and the difficulty in maintaining the viruses' integrity during air sampling methods.

Implications of Airborne Transmission

Due to the surge of research pointing towards the possibility of aerosol transmission, there is the prospect that our current control measures are inefficient at mitigating the spread and might need reconsideration. In this section, we review some of the implications of SARS-CoV-2 being an airborne disease.

Ventilation

Ventilation is defined as the inflowing and distribution of air into a confined space between walls or between rooms in a closed building. The ventilation rate is the amount of outdoor air introduced per unit time, and the distribution refers to the direction of flow of this air[133]. The latter can be affected by outside factors such as the movement of the host, the opening of windows and doors, or air-conditioning[133]. In outdoor settings, social distancing rules might be sufficient. Conversely in more confined spaces, people are in closer proximity and the dilution of viral concentration is less applicable, making the susceptibility to the contagion much higher[134,135]. The possibility of transmission is affected by different factors including indoor airflow, where it can affect the movement of aerosols between the infected source and the host[136]. As previously mentioned, aerosols can linger in the air for longer and are susceptible to drifting farther away than droplets can[76]. When we speak of droplets, they tend to decrease in concentration after emission from the source of infection within 1 to 1.5 meters, as they drop to the ground or other surfaces, which makes it easier to avoid with regular social distancing rules[137]. However, aerosols do not tend to sink to the ground as droplets do and may stay suspended in the air for longer[137]. Being more technical, under the influence of gravity, indoors, and where the air is still, exhaled particles with diameters of 5-10 µm fall to the ground. This would take about 8-30 minutes from a height of 1.5 meters. The majority of rooms though have typical ambient air currents of 0.1-0.2 m/s, which makes it more difficult for these small particles to settle on the ground from a 1 to 2 meters source. In indoor settings, they must be larger than 50-100 µm to land within 1 to 2 meters from the source. It is well agreed that any droplets beyond the size of 50-100 µm can be swept in a jet of exhaled air, particularly during sneezing or coughing, beyond 1 to 2 meters[138,139]. If we were to compare a well-ventilated room with a non-ventilated room, we would see that aerosols in the latter remain in the air, with one being at risk of inhaling them for longer. While a well-ventilated room would replace the air, with the virus-containing aerosols, removing this risk[137]. For example, in a study where droplet production with coughs and sneezing was analyzed, it was found that in the best-ventilated room, the dispersion of droplets had lessened by half, whereas, 5 minutes were needed to disperse the droplets with no ventilation at all. This is important information due to the fact that an infectious dose in the air can build up over time. Consequently, ensuring sufficient and effective ventilation in common spaces and buildings is of utmost importance[72]. This can be implemented in a cost effective, practical, and easy way. It is also important to take into consideration the guidelines put forth by organizations such as the American Society of Heating, Ventilating, and Air-Conditioning Engineers (ASHRAE), and the Federation of European Heating, Ventilation, and Air Conditioning Associations (REHVA), on the use of HVAC systems[72,140,141]. More thought might be needed to be put into avoiding contaminated air being circulated multiple times with the use of filtration systems and disinfection[141], such as with ultra-low particulate air (ULPA) filters or electrostatic precipitators (ESPs)[135]. Air purifiers that use HEPA for filtration can also be taken into consideration, which has been proven to be efficient enough to remove virus-laden aerosols and provide clean air back into the circulation[133].

Hospital Settings and Aerosol-Generating Procedures (AGPs)

Nosocomial infections are quite common, and most hospitals require six air changes per hour (ACHs) in clinic rooms and a minimum of 15 ACHs in operating rooms (ORs), of which three of those changes are replaced with outdoor air[136]. This is highly important especially during peak seasons of any airborne disease, where there is a prevalence of infected patients spreading bio aerosols and AGPs are typically on the rise[142]. Such procedures are defined by the CDC as procedures that can cause the formation of uncontrolled emissions of respiratory secretions in amounts more than coughing, sneezing, talking, and breathing can cause[136]. Examples of such procedures include but are not limited to, intubations, bronchoscopies, cardiopulmonary resuscitations, sputum inductions, chest physiotherapy, nebulizer administration, and dental procedures[67,136,143]. In a study on dental procedures[144], a method of lessening AGPs was suggested through the addition of water and high molecular weight FDA-approved polymer during irrigation processes in the clinic. This could reduce or even eliminate droplet formation by the commonly used rotary or ultrasonic instruments dentists use. This can possibly also be used in general medical procedures other than in dentistry. It does not disinfect or inactivate viruses, and PPE would still be needed, nonetheless, it could lessen their presence[144]. Negative pressured rooms can also be used as another layer of protection. In this instance, COVID-19 patients are placed in rooms where the air pressure within them is lower than the surrounding rooms or areas. When the door of such a room is opened, contaminated air cannot exit into the surroundings, which protects other individuals not working closely with the patients[145]. It is also highly important that laboratories in hospitals or research centers be of a certain biosafety level (BSL), that is suitable for the risk of microbes being worked on. For example, when isolating the SARS-CoV-2 virus or using the PCR test, a laboratory with BSL-3 levels must be used[146]. These laboratories come with a set of standards other than just using personal protective equipment. For example, there needs to be accessibility to hands-free sinks and eyewashes, directional airflow bringing in clean air into the laboratory, and interlocking doors, where access to general building corridors or common areas is limited to avoid leakage of contaminated air[147].

Transportation

Having your private transportation is optimal when it comes to social distancing, however, not everyone has access to such luxury, and the negative impacts on the environment make public transportation and carpooling more appealing to reduce emissions. In a study by Mathai et al[148], the in-cabin climates of a car were numerically assessed to be able to attenuate the elevated risk of transmission inside a vehicle[148]. Ventilating the car by opening all windows was found to be the best method of mitigating risks by allowing the direction of air to travel across the cabin, away from the occupants, and exit through the rear windows[76,148]. This allows the isolation of the left and right sides of the cabins from each other, which points towards the best seating arrangement of people to be on opposite ends if possible[148]. As aforesaid, there is also a risk in buses. Considering the space in a bus, ventilation techniques such as those used in a car might be beneficial. In airplane cabins, there are about 20-30 ACHs[148] and HEPA filters are used. There needs to be extra caution in maintaining the filtration system to function at optimal levels, and maybe an increase in ACHs.

Personalized Ventilation

Although not as common as other modes of ventilation, one proven way to improve infection control by a factor of 35 is based on the projection of jets of air onto an infected person's face[149-151]. This encompasses wearing a device on one's head, which emits a jet of air that redirects any expelled droplets or aerosols away from the person they are facing[151]. Of course, this would work best in settings where a person is stationary, such as in a care home, clinic room, or at home[152]. There have not been enough studies on this type of ventilation system. Hence the possibility that the aerosols are still redirected to other parts of a confined space, rather than being restricted to around the infected person. That being said, it could be possible for short-term use to keep the air between two persons decontaminated.

Educational and Workspaces

In such spaces, ensuring that ventilation and filtration systems are up to par is most paramount[153]. Filters with a Minimum Efficiency Reporting Value (MERV 14) rating of 14 can be used to reduce any contamination between different rooms, such as in the case of offices and classrooms[154]. Good room air distribution must be taken into account for open classrooms and workspaces. For example, using mixing ventilation (MV), for the delivery of fresh air while taking into account the guidelines given by ASHRAE[155,156]. Even better than that is displacement ventilation, where the cool supply of air is delivered at a level close to the floor, and the exhaust is located closer to the ceiling[155,156]. Semi-open partitions or screens between people can be used to give each person their personal space, which would be useful in reducing cross-contamination by breaking the air distribution patterns[140,153].

The Wearing of Masks

The main premise behind wearing a mask is weakening the force of the exhaled breath, thereby reducing its mixing with surrounding air that others would inhale[151,153]. Masks can also break the trajectory of droplets formed during coughing or sneezing; however, this does not apply to aerosols in regular surgical masks[76,151]. Surgical masks may be suitable to reduce viral load in airborne transmission, but not infection all together[151]. Convection and diffusion can still emit aerosols outwardly from behind the surgical mask, which is why proper fitting of the mask is very important. Respirators, such as the N95, which are more fitting and better at removing fine droplets should be considered[151]. With the aforementioned steps taken into consideration, the efficiency of a mask against SARS-CoV-2 depends on how well the material of the mask can filter air, their fitting, and how effective they are at preventing peripheral leaks[157]. Medical staff, especially those treating COVID-19 patients, are better protected with N95 masks or even doubling up on a surgical mask under an N95. One important technique to consider is getting fit-tested for the mask since spaces between the face and the mask itself put one at risk[158,159].

Climate and Environmental Factors

The prevalence and outcomes of COVID-19 have varied significantly from country to country. There are multiple factors at play here and one could be the climate. It has been revealed that weather and environmental conditions might contribute to the risk of retaining viral infectivity in aerosolized droplets[160]. Schuit et al[160] suggested that the environmental conditions might affect the SARS-CoV-2 ability to transmit via aerosols. They noted that the virus-laden aerosols generated from simulated saliva were rapidly inactivated by simulated sunlight[160]. Dbouk and Drikakis[161] developed a theoretical simulation for fluid dynamics to study the impact of different weather conditions on the virus's transmission and viability. They revealed that at high relative humidity, the virus-laden aerosols could travel for long distances, and the virus could stay infectious at high concentrations. Whereas at high temperatures and low relative humidity, the virus could lose its infectivity in aerosols[161]. There also seems to be evidence that transmission rates are lower in hotter environments, pointing towards the seasonality of transmission. If this is true, then acting to mitigate the virus could differ from season to season. As previously mentioned, quite a few studies[106-111] have also pointed towards SARS-CoV-2 containing aerosols being suspended in polluted air for longer than less polluted air, which raises the question of whether lessening pollution could be the answer to mitigating viral spread to some degree[162].

Inactivation and Disinfection

As mentioned in the previous section, one of the most effective strategies of inactivating SARS-CoV-2 in aerosols is through sunlight[160]. This means that letting in sunlight into a vehicle, home, or office could be an effective way of naturally getting rid of infected aerosols[160]. As an antiseptic technique, the ultraviolet-C (UV)-C emitting radiation technology can be used to mimic the effects of sunlight and rid whole areas of any active SARS-CoV-2 aerosols, alongside UV-B radiation[160,163]. Fogging machines can also be used in public spaces dispersing a mist of disinfectant[157]. The aerosolization of the disinfectant means that they can be suspended in the air for longer durations, increasing the probability that they collide with SARS-CoV-2 containing aerosols[157]. Another active area of research is the disinfection of PPE using microwave-generated steam, and other methods of dry heat. There seem to be some positive results, although more research needs to be done. Nevertheless, if proven to be effective, these methods could possibly also be used to decontaminate larger spaces[164].

Lessening Transmission from the Source

Altering or modifying the properties of mucus can aid in lessening the transmission from an infected person, meaning that the aerosols emitted from a person breathing or speaking can be reduced[165,166]. This can be done by the administration of 1 gram of isotonic saline orally, possibly reducing exhaled aerosols by 72%[166]. There are also studies on the use of povidone-iodine against SARS-CoV-2, inactivating it after contact of 15 seconds in vitro[167]. Since the virus resides in the nasal cavity, nasopharynx, oral cavity, and oropharynx, gargling or using a nasal spray consisting of povidone-iodine may also lessen the emission of the virus-containing aerosols from the infected person[168,169].

Public Toilets

One often overlooked route of transmission is toilet flushing, which can generate droplets that can turn airborne[170]. COVID-19 patients often suffer from gastrointestinal symptoms and can shed the virus in their stool[170]. There needs to be more awareness on the subject and for the common person to exercise precautions such as putting down the toilet lid when flushing, using disinfectants in the toilets as one flushes, or even using non-flushing commodes in healthcare settings[170].

Discussion

It is difficult to ascertain that the airborne transmission route is an efficient one, even with a plethora of evidence pointing towards it being a possibility; however, correlation does not always mean causation. Drawing firm conclusions regarding the airborne transmission of SARS-CoV-2 has been difficult, due to the lack of viable virus with considerable infectious load in many cultured samples, and the lack of consistency in methodology between studies[171]. One important yet forgotten perspective is that the traditional definition of airborne transmission has led to much of the current debate. Airborne particles do not necessarily have to be small in size to travel in the air for long distances. Inhaling virus-laden particles of whatever size, directly from the air, can be considered to be an infection through the airborne route. Large droplets can also travel for long distances with the assistance of airflow dynamics and stay suspended in the air[172,173]. In short-range transmission, small-size aerosols occur at much higher concentrations close to the source and can be directly inhaled, so the airborne transmission does not happen solely over long ranges[173]. From the studies discussed in the previous sections, reporting infections with no observed physical or close contact, from asymptomatic or presymptomatic sources, in the absence of coughing or sneezing, and mostly indoors, can lead to the assumption that airborne transmission of SARS-CoV-2 exists. Besides, reporting nosocomial infections while making proper use of precautionary measures and PPE against droplet transmission also indicates the possibility of SARS-CoV-2 infections through airborne means. On the other hand, failure to detect the virus in the air samples, or failure to cultivate it does not mean it is not airborne. If viral RNA is detected from air samples, it is better to err on the side of caution and consider it an indication that it is more likely that live virus is present than not, which in turn imposes effective infection control[84]. As previously stated, quite a few researchers were capable of growing SARS-CoV-2 from air samples using tissue culture. Such examples include studies done by Ladnicky et al[89] and Santarpia et al[90], whereby they collected air samples from hospital rooms of COVID-19 patients[89,90]. It is very difficult to detect viable viruses with enough infectious load from the air, as many technical issues interfere and halt this process. For example, less efficient sampling methods, viral dehydration, damage during sampling and collection, and retention of the virus in the sampling apparatus could make this difficult[174]. Environmental factors, such as relative humidity, radiation, composition of the air, and temperature can also have an effect, as the structure of the virions is not rigid enough to survive such conditions[175]. This is why detection of viruses using molecular methods is more sensitive than isolation of viruses via cell culture. Also, more than one virus is needed to initiate infection in a cell culture[172]. For instance, Fabian et al[176] using the Influenza virus found that one $TCID_{50}$ represents approximately 300 genome copies[176]. This estimate is within the same range as Van Elden et al[177] estimate of 100-350 copies, however, much less than 650 copies reported by Wei et al[177,178]. As the inability to recover viable viruses has limited the supporting evidence, it is important to realize that there is also insufficient evidence to disprove the hypothesis of airborne transmission. For example, Wong et al[127] studied the transmission of SARS-CoV-2 from one admitted index patient by tracing and testing all his contacts[127]. Although all of them were negative for SARS-CoV-2, it was peculiar that many of them had developed symptoms. Furthermore, the inability of the researchers in this case to find any positive cases cannot alone exclude the possibility of airborne infection found in other scenarios, especially that confounding factors such as ventilation were not taken into account[127]. In another study by Chia et al[83], air samples tested positive for SARS-CoV-2, but on the contrary they still concluded that there was not enough evidence to prove that aerosols were a key route of transmission, without even culturing their samples for further confirmation[83]. Moreover, environmental factors such as temperature and relative humidity, and the application of enough precautionary measures of disinfection and well ventilation might play an important role in inactivating the virus and lowering its transmission. Although experimental investigations using artificial and dynamic models have played a role in trying to prove airborne transmission, real-life scenarios vary in comparison to artificially made and laboratory-controlled conditions. For example, the artificial saliva and emission jets trying to replicate human coughing and sneezing. In contrast, the flow velocities of natural human inhalations and exhalations are much lower, which means that expelled viruses are less likely to be damaged by shear stress[179,180]. Tang et al[181] ranked the weight of evidence of SARS-CoV-2 aerosol transmission an 8 out of 9 according to the criteria by Jones and Brosseau[181]. Their criteria of aerosol transmission suggest that an infected person needs to generate the virus-containing aerosols, the particles need to retain infective viral matter for long periods of time, and that the aerosols can reach a target host and infect its tissue with enough viral load, which in our opinion are quite robust indications[19,181].

Conclusions

Although this review has not concluded whether airborne transmission of SARS-CoV-2 is the main route of transmission, there is still a high risk that SARS-CoV-2 can remain suspended in the air for long periods of time and inhaled by others even after distancing from the infected person. More research needs to be done on whether any suspended aerosols have a high enough titer of SARS-CoV-2 that can lead to infection upon inhalation. It is a good idea to take preliminary precautions with regards to ventilation, inactivation, and reduction of emission from infected people regardless of transmission routes, as they could work effectively against both droplets and aerosols. Governments can also play an important role by helping the public make informed decisions and calculated risks on how to socially distance, work, and what kind of protection to use. This can be done by the adoption of campaigns, marketing, and educational clips as we have seen many countries are actively doing.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

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