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Review

SARS-CoV-2 aerosol transmission and detection

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ABSTRACT

Aerosol transmission has been officially recognized by the world health authority resulting from its overwhelming experimental and epidemiological evidences. Despite substantial progress, few additional actions were taken to prevent aerosol transmission, and many key scientific questions still await urgent investigations. The grand challenge, the effective control of aerosol transmission of COVID-19, remains unsolved. A better understanding of the viral shedding into the air has been developed, but its temporal pattern is largely unknown. Sampling tools, as one of the critical elements for studying SARS-CoV-2 aerosol, are not readily available around the world. Many of them are less capable of preserving the viability of SARS-CoV-2, thus offering no clues about viral aerosol infectivity. As evidenced, the viability of SARS-CoV-2 is also directly impacted by temperature, humidity, sunlight, and air pollutants. For SARS-CoV-2 aerosol detection, liquid samplers, together with real-time polymerase chain reaction (RT-PCR), are currently used in certain enclosed or semi-enclosed environments. Sensitive and rapid COVID-19 screening technologies are in great need. Among others, the breath-borne-based method emerges with global attention due to its advantages in sample collection and early disease detection. To collectively confront these challenges, scientists from different fields around the world need to fight together for the welfare of mankind. This review summarized the current understanding of the aerosol transmission of SARS-CoV-2 and identified the key knowledge gaps with a to-do list. This review also serves as a call for efforts to develop technologies to better protect the people in a forthcoming reopening world.

1. Introduction

In human history, there has been an evolving understanding of the airborne transmission of infectious diseases [1–6]. Back in the AD 100–200, a miasma theory proposed by Roman physician Aelius Galenus described the airborne transmission of infectious diseases. Then about 500 years ago, Italian physician Girolamo Fracastoro (1478–1553) stated in his book that airborne tiny particles can cause epidemic diseases over a distance. Later, Louis Pasteur (1861) discovered viable microorganisms in the air that could propagate under nutrient conditions [7]. It is now known that the air we breathe consists of microbes, either viable or dead, together with their derivatives such as endotoxin and allergens [8,9]. With every breath, we inhale various microorganisms from the air. When a pandemic occurs, airborne transmission of certain respiratory viruses could quickly dominate the spread [4,10]. In addition, climate change further deteriorates air pollution, and the frequency of infectious outbreaks also increases [11,12]. It has been long anticipated that there will be a global infectious disease outbreak in the distant future [13]. Such a moment, the COVID-19 pandemic, finally struck the world three years ago. As of April 20, 2022, more than 504 million COVID-19 infections including 6.2 million deaths, were reported [14]. As of April 17, 2022, a large fraction of people in the world had already been vaccinated with a total of 11.3 billion doses of vaccine administered globally [14]. Unfortunately, studies have shown that vaccinated people could still get infected by variants of SARS-CoV-2 [15,16]. In the coming months, people are still afraid of society reopening after the pandemic hit [17,18]. How to effectively prevent infection of COVID-19 is a rather important question in the face of a complete reopening global economy.

Aerosol transmission plays a major role in many large-scale infectious disease outbreaks, including COVID-19 [10]. Developing a better understanding of the role of aerosol transmission of SARS-CoV-2 can help counter the threat. On the other hand, SARS-CoV-2 aerosol detection can serve as a "smoke detector" for COVID-19 such that early-stage control measures can be implemented before the disease starts spreading further in the community. Additionally, rapid screening of people for COVID-19 can help locate the infected in time. Currently, effective control often requires lengthy quarantine, which is difficult to implement for the reopening economy. People would face greater risks of COVID-19

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infections in the opening economy. On-site SARS-CoV-2 monitoring and rapid COVID-19 screening are two key technological shields for protecting people from infection in combating the pandemic. However, these two critical components are under-studied and need to be rapidly developed in the face of massive challenges for reopening the economy. Time for these efforts is rather limited, and key actions must be taken immediately. However, all these developments require a deep understanding of the key issues relevant to aerosol transmission. Here, a review was conducted to summarize current advances in understanding the problems and technological solutions and to identify the key knowledge gaps with a to-do list for combating the COVID-19 pandemic.

2. SARS-CoV-2 emission and aerosol transmission

COVID-19 patients were found to emit millions of SARS-CoV-2 particles per hour, especially during the early stage of the disease [19]. SARS-CoV-2 concentration levels in the exhaled breath condensate were also shown to vary among individuals [19]. SARS-CoV-2 can be released via exhalation, talking, coughing, sneezing, or other means into the environment, for example, directly into the air, onto surfaces, or into wastewater [20–23]. Those deposited on surfaces could be re-aerosolized into the air upon evaporation and walking disturbance [24–26], while those in the water could also be re-aerosolized into the air, for example, during the toilet flushing process [27]. Leung [28] provided a thorough review of different transmission modes. In the aerosol science field, we refer to aerosol as a mixture of particles of less than 100 μm in a gaseous medium [29]. Here, we use the term from the aerosol science community to describe disease transmission, referring to not just those of less than 5 μm, but also larger ones (<100 μm). Accordingly, the air is a vital exposure route to SARS-CoV-2 for humans.

As of this writing, the SARS-CoV-2 emission patterns remain unclear. He et al. [30] reported that the highest viral load in throat swabs was observed at the time of symptom onset, and transmission of COVID-19 occurred at the presymptomatic stage. Ma et al. [19] also showed that COVID-19 patients in the early stages emitted more viral particles than the late ones. Some studies showed that the infectiousness increased about 1–5 days after symptom onset of COVID-19 [31], which varied greatly among individuals [31,32]. In our previous work, even right before the hospital discharge, the COVID-19 patients' exhaled breath still contained SARS-CoV-2 RNA [22]. Our previous studies have shown that human breathing produces particle emissions of 1.5 μm peak size [33]. Fennelly [34] reviewed available studies and found that cough aerosols and those of exhaled breath from patients with various respiratory infections had similar aerosol size distributions, that is, a predominance of pathogens in small particles (<5 μm). However, the expelled particle size distribution of aerosols from COVID-19 patients is still not available at the time of this writing. Zhao et al. [35] found that speech-generated droplets can spread three times farther in low-temperature and high-humidity environments, and in contrast, the number of aerosol particles increases in high-temperature and low-humidity environments. SARS-CoV-2 emissions depend on many different factors, for example, disease stage, time of the day, medication use, age, etc. [19,36,37]. Accordingly, SARS-CoV-2 emission uncertainty impacts the polymerase chain reaction (PCR) test.

Airborne SARS-CoV-2 emission plays a very important role in the COVID-19 transmission. After a long, heated debate, the WHO finally stated that the airborne route is an important transmission route for COVID-19. In contrast, studies have indicated the fomite-facilitated transmission plays a minor role in the COVID-19 pandemic [38,39]. Central to the debate is the difference in the definition of aerosol and droplet [1]. It is now widely accepted that aerosol transmission plays a very important role in this pandemic. There is a collective call for controlling indoor respiratory infections through both ventilation and engineering control methods [2]. In the future, building design should take into account aerosol transmission, for example, ventilation, solar inactivation of pathogens, and a toilet system that minimizes aerosol transmission. It is time to re-consider this important indoor health problem. If the aerosol transmission can be better controlled, the impact of the pandemic could be substantially minimized.

3. Microbial aerosol sampling

3.1. Bioaerosol sampling

SARS-CoV-2 aerosol monitoring is critical to guarding the air. Among others, sampling is the first step for characterizing the risk. Over the years, many efforts have been devoted to air sampling for viruses, bacteria, fungi, and other biological aerosol materials [40]. There are many different types of samplers for collecting bioaerosol particles. Each one has its own advantages and disadvantages [41]. Virus sampling usually requires a very low cutoff size (the particle size at which the sampler has a 50% collection efficiency) because the viral particles are usually much smaller than bacteria and fungi. When the viral particles are released into the air from human breath, they evaporate and are diluted quickly by the atmosphere. Accordingly, a large air volume has to be collected to enrich enough viral nucleic materials for PCR amplification. Additionally, since the air is moving even in indoor environments and so do particles, the air sampling has to be very rapid so that enough air volume can be obtained in a very short period. Despite the high physical collection efficiency of filtration, collecting a large air volume is a great challenge due to its low sampling flow rate and high pressure drop. In addition, the strong physical desiccation from the filter is another problem, especially for viral infection studies. A liquid sampler can somehow satisfy both high volume and viability preservation requirements.

3.2. SARS-CoV-2 aerosol sampling

During the early stages of the COVID-19 pandemic, our research team has employed a robot-assisted cyclone sampler for automatic sampling of airborne SARS-CoV-2 in hospital environments [22]. We have successfully collected SARS-CoV-2 with a concentration level of 9–219 RNA copies/m^3 [22]. The air sampler collected 18 m^3 of air from 40-min sampling. In another independent work, the cyclone sampler also successfully collected SARS-CoV-2 with a level of 1.11×10^3 to 1.12×10^4 RNA copies/m^3 [42]. Other teams have used filters, e.g., gelatin filters, which needed a longer sampling time (e.g., up to 20 h) to obtain enough volume of air [25], and a ventilation duct to collect the virus [19,22,43,44]. In another work, sampling with a high flow rate (50 L/min) filter was also used for detecting SARS-CoV-2 [45]. These methods have their own advantages and depending on the actual situation the desired sampling method can be selected. The use of a ventilation duct is similar to an air sampler, but it is difficult to quantify the viral level in the air. However, in order to obtain a result in a very short time, a large volume of air by rapid sampling is certainly preferred. When designing a sampler, ideally both physical and biological collection efficiency should be considered. As discussed above, a critical parameter for characterizing a sampler's physical efficiency is its cutoff size. Biological collection efficiency, on the other hand, refers to its ability to collect viable biological aerosol particles.

Similar to wastewater-borne viral monitoring [46], SARS-CoV-2 aerosol sampling in a public space can be used as a pooled sample of exhaled breath from many different people who spent time in the environment. Therefore, one air sample can serve as a surrogate sample for many people in an enclosed or semi-enclosed space. SARS-CoV-2 presence in the air sample means that there might be a COVID-19 patient who spent time in the studied environment. For example, a liquid sampler (Beijing BioCTech Co. Ltd) was employed to monitor SARS-CoV-2 aerosol in Beijing Winter Olympic Games. SARS-CoV-2 in the air is usually diluted and dispersed over time, thus a method with a lower detection limit is desired in order to detect a minute number of viral particles. Air sampling and detection together can serve as a warning for air safety so that disinfection and control measures can be mounted immediately

before any further spreads. Future sampling protocol needs to be designed so that the infectivity of viral particles can be better preserved for subsequent infectivity analysis. In addition to environmental monitoring, wearable sampling devices can also be developed for personal breathing zone monitoring to assess the personal exposure risk. In the pandemic era, SARS-CoV-2 aerosol monitoring becomes particularly important and can be used for the early detection of a potential COVID-19 outbreak.

4. SARS-CoV-2 aerosol detection strategy

4.1. Nucleic acid-based SARS-CoV-2 aerosol detection

There is a heated debate about the aerosol transmission of COVID-19. This debate is largely due to the differences in disciplines and the lack of aerosol detection methods. Unlike pollutants in other media, airborne pollutant detection has to come with well-performed air sampling first. For SARS-CoV-2 aerosol detection, the common practice is to combine air sampling with a nucleic PCR test. With respect to sampling, a momentum was observed that a cyclone liquid sampler with a high flow rate is generally preferred to collect SARS-CoV-2 aerosol, especially in China. As for RT-PCR tests, they have been reported to fail to detect SARS-CoV-2 in many air samples due to their high detection limits [19,22,25]. Occasionally, air samples collected from toilets (a confined and enclosed environment) were tested positive by RT-PCR with a higher viral RNA level [19,45]. On the other hand, Loop-mediated isothermal amplification (LAMP) has a relatively lower detection limit and a higher sensitivity, and has been increasingly used for detecting SARS-CoV-2 [47]. Indeed, it can be used together with air sampling for SARS-CoV-2 aerosol detection, which can provide an early warning for a potential COVID-19 outbreak.

4.2. Other sensors and detection methods for SARS-CoV-2

Concurrently, other studies investigated the use of immune-based, nanosensor, and optical methods for rapid SARS-CoV-2 detection [48–50]. These technologies, although ultra-sensitive and fast, have not been utilized in the real-time monitoring of SARS-CoV-2 aerosol. Practically, online detection of SARS-CoV-2 can be very useful in guarding air safety in public domains. Airborne detection of pathogens has been a long-standing challenge for many years. Shen et al. [51] have integrated air sampling, microfluidics, silicon nanowire sensing, and electronics for real-time monitoring of airborne influenza virus. The system translates airborne biohazard into a viewable electrical signal which renders humans equivalently equipped with additional "sensing capability" for the airborne biohazard. Many similar nano-enabled technologies can be utilized for SARS-CoV-2 detection when coupled with air sampling for aerosol [52]. Similarly, this can also be achieved for real-time monitoring of SARS-CoV-2, as illustrated in Fig. 1. The air is continuously sampled, and transported by a peristaltic pump via microfluidics into the antibody-decorated sensor area. Whenever there is SARS-CoV-2 in the air, the sensor would generate a viewable electrical signal that can serve as an alert. Such technologies may have great potential in combating airborne infectious disease threats, for example, this COVID-19 pandemic. Yet, there is still a long way from the laboratory to practical sensing. With challenges from COVID-19, this area of research now would certainly need to move faster than any other time.

Ideally, a wearable sensor device can be developed to alert potential exposure risks. Relevant technologies are already there, and what needs to be done is to integrate various elements and optimize the performance. For example, a wearable device was developed for sensing SARS-CoV-2 by integrating several elements such as substrates and textiles functionalized with freeze-dried, cell-free synthetic circuits, and CRISPR-based tools [53]. At the same time, antibody-based sensing needs robust virus receptor and background noise reduction algorithms. Additionally, better sensing sample pretreatment technology might also be required after the sampling to enhance the detection capability. On-site stable and reliable detection of SARS-CoV-2 aerosol in real-time could play a critical role in guarding against the pandemic. Unfortunately, such a system is still in its bench stage as of this writing.

Air is a complex mixture of thousands of different biological and non-biological pollutants, and many of them are not identified due to the lack of analytical power. The guard against air toxicity is a significant challenge not only for now but also in the future. Toward this end, a recent work has demonstrated some promise of real-time monitoring of air toxicity by utilizing volatile organic compounds (VOC) profile emitted by a mouse when exposed to different toxic substances [32]. They have shown that whenever the mouse was exposed to a toxic airborne substance, it would release a distinctive profile of VOC fingerprints within a very short period. If further improved and optimized, the system could monitor those unknown human pathogens. This type of sensing represents a future need for comprehensive air toxicity monitoring.

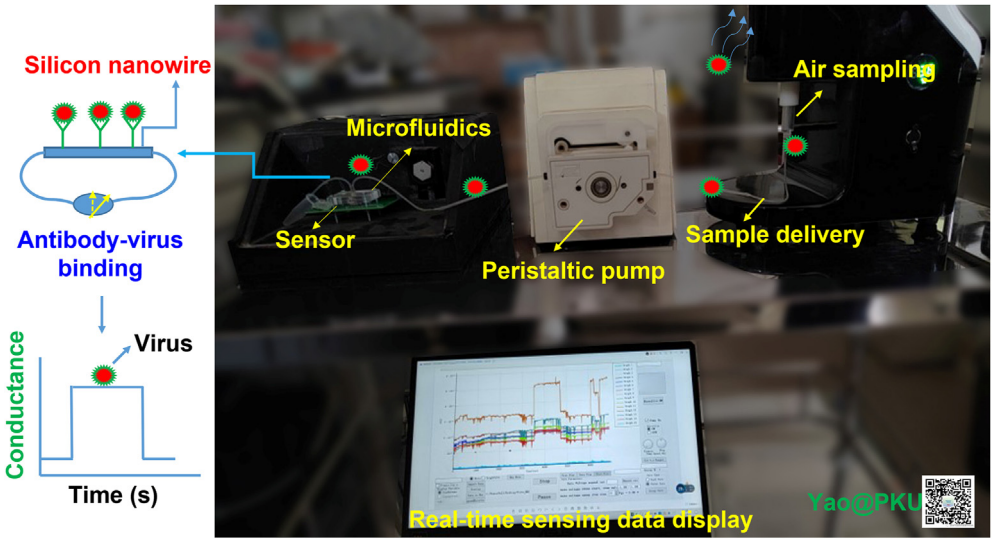

Fig. 1. Integration of commercialized technologies, including air sampling, microfluidics, and antibody-decorated silicon nanowire sensor for real-time monitoring of SARS-CoV-2 aerosol (photo provided by the author).

5. SARS-CoV-2 aerosol viability and infection

5.1. Impacts of environmental parameters on SARS-CoV-2 infection

Infection by SARS-CoV-2 depends on the dose and viability of SARS-CoV-2. For potential SARS-CoV-2 aerosol exposure, the concentration decreases over a longer distance from the source. The overall dilution depends on the dimension of the indoor environments and the ventilation characteristics. Increasing ventilation and distance would substantially decrease the viral aerosol level, thus reducing the potential dose. SARS-CoV-2 viability is equally important for establishing an infection. The SARS-CoV-2 was shown to remain viable for a sustained period of up to 16 h in respiratory size particles [54]. In other studies, viable SARS-CoV-2 was also recovered from hospital environments [55], passenger cars [56], and respiratory mask surfaces [42]. When the virus is released into the air, its surface spike protein would be in contact with air pollutants (particles and gaseous pollutants such as ozone, NOx, etc.). Likewise, the virus would be also surrounded by ambient pollutants when deposited together inside the lung. During the initial phase of the pandemic, Yao et al. [57] analyzed the effects of environmental parameters such as ozone, humidity, and temperature on the COVID-19 spread. It was shown that the number of COVID-19 cases increased with decreasing ozone levels (94.67–48.83 $\mu g/m^3$). By contrast, the number of cases increased with increasing relative humidity (23.33%–82.6%) but decreased with increasing temperature [57]. Ozone was verified to inactivate SARS-CoV-2 effectively [58,59]. Other studies showed that ultraviolet-C (UV-C) can efficiently inactivate SARS-CoV-2 [60,61]. These environmental parameters together play a role in the viability of SARS-CoV-2 aerosol. Thus, cities with different matrices of these parameters could have different COVID-19 transmission potentials. Because of damages from air sampling, culturing SARS-CoV-2 is difficult. Breathing by people is also a process of "air sampling" by which airborne particles deposit into the lung, but it is gentler compared with air sampling with minor damages to the virus viability. Nonetheless, sharing both space and time with COVID-19 patients would significantly increase the infection risk. This, on the other hand, could explain the discrepancies among the effects of environmental parameters, air sampling, and inhalation on the SARS-CoV-2 viability and infection.

5.2. SARS-CoV-2 aerosol viability

The viability and culturability of SARS-CoV-2 are largely related to its receptor-binding domain (RBD) residing on the spike protein, which binds to the human angiotensin-converting enzyme 2 (ACE2) receptor [62]. Anything that can influence the binding of the RBD with ACE2 impacts the cell entry ability of SARS-CoV-2 and its infection. As mentioned above, SARS-CoV-2 in the air could interact with atmospheric pollutants. Among them, some species such as ozone could directly degrade viral coat proteins and disrupt the viral structures, thus rending the viability loss [63]; while some other species could alter the receptor characteristics of the viral surface [64]. These interactions would lead to the inability of SARS-CoV-2 binding to ACE2, thus limiting the infection. Watzky et al. [65] have reported that 50 chemicals in the air modulate the expression of ACE2 or human proteases that are important for SARS-CoV-2 cell entry. They have further demonstrated that environmental exposures could influence the expression of genes involved in viral cell entry. Of course, atmospheric pollutants might also impact other properties of SARS-CoV-2, such as the replication potential through damaging the viral RNA by atmospheric radicals. Woodby et al. [64] provided a detailed analysis of the influences of air pollutants on the pathogenesis and replication of SARS-CoV-2. An association of an increase in $PM_{2.5}$ level with a higher infection rate of COVID-19 was also detected [66,67]. However, no experiments were conducted to investigate the impacts of $PM_{2.5}$ on the viability of SARS-CoV-2.

Apparently, there is a lack of active collaboration between virologists and environmental scientists. Virologists are generally not aware of the impacts of airborne pollutants on SARS-CoV-2, while environmental scientists do not have the facility such as BSL-2 or that with a higher safety level and resources to conduct relevant experiments. Certainly, more efforts should be devoted to investigating the influencing factors on the viability of SARS-CoV-2 in the air, which is critical to establishing an infection. The discovery of such factors can guide engineering design solutions for the indoor environment. This could help make a huge difference in defeating the pandemic, especially in a reopening economy. Nonetheless, the study of the viability of airborne SARS-CoV-2 requires a better sampling method.

6. Experimental and epidemiological investigation of aerosol transmission of SARS-CoV-2

Since the pandemic, many teams have carried out epidemiological investigations for outbreaks. Environmental transmission plays an important role [68], especially the airborne route. Recently, in Guangzhou COVID-19 outbreak, there was a simulation report that the COVID-19 was transmitted between two "handshake" buildings (i.e., buildings that are very close to each other) via an airborne route [69]. An overseas traveler stayed in an observation room waiting for his RT-PCR test results, while simultaneously transmitting the SARS-CoV-2 into the room of another close building (about 0.5 m distance) across the space between the two buildings. A lady in the other building got infected via inhalation of the transmitted viruses. A gas tracer study led by our group on May 29, 2021, has found that the exhaled virus can be easily transmitted into the other building, as demonstrated in Fig. 2. About 5%–18% of the tracer gas released at location A entered the clinic room in Building #2. According to the epidemiological report, the lady who got infected did not have any previous close contact with the COVID-19 patient. This outbreak presents strong evidence for aerosol transmission of COVID-19. In a bus COVID-19 outbreak, the airborne spread of SARS-CoV-2 was likely to contribute to the high attack rate [70]. The central air conditioners for both buses were in indoor recirculation mode. Many more similar outbreaks point to the airborne transmission of COVID-19 [71,72]. Epidemiological evidence for airborne transmission sometimes requires solid proof from the nucleotide sequence of SARS-CoV-2 in samples from different COVID-19 patients. For example, a study has linked the COVID-19 outbreak to environmental transmission via cold-chain food supply, which did not exclude the possible aerosol transmission in Xinfadi Market in Beijing based on sequencing data [73]. However, the air is moving, and *in-situ* direct evidence cannot be obtained for humans for ethical reasons.

Since the pandemic, many studies have presented evidence of airborne transmission of COVID-19 using animal models [74,75]. For example, Kutter et al. [76] have shown that both SARS-CoV and SARS-CoV-2 can be transmitted through the air between ferrets over more than one-meter distance. It is a challenge when epidemiological investigation for environmental transmission is conducted to trace the transmission routes where both surface-borne and airborne could be simultaneously involved. For example, Li et al. [77] provided both epidemiological and genome evidence about the environmental transmission of COVID-19 but could not differentiate between airborne and surface-borne transmission. Another difficulty is the culturing of SARS-CoV-2 in environmental samples (air and surface swabs). Currently, there is still limited information and understanding about how long SARS-CoV-2 residing on the surface or in the air remains viable in real-world scenarios, and when the loss of viability occurs, for example, in the media itself or during the sampling process. Additionally, factors involved in recovering viable SARS-CoV-2 from the air samples are largely unknown. These factors altogether complicate the environmental (via air or surface) transmission investigation. The exact inhalation dose of airborne SARS-CoV-2 required for establishing an infection is not known either. These critical questions hamper a better understanding of the airborne transmission of COVID-19. These questions are also central to the debate on aerosol transmission, which however receives

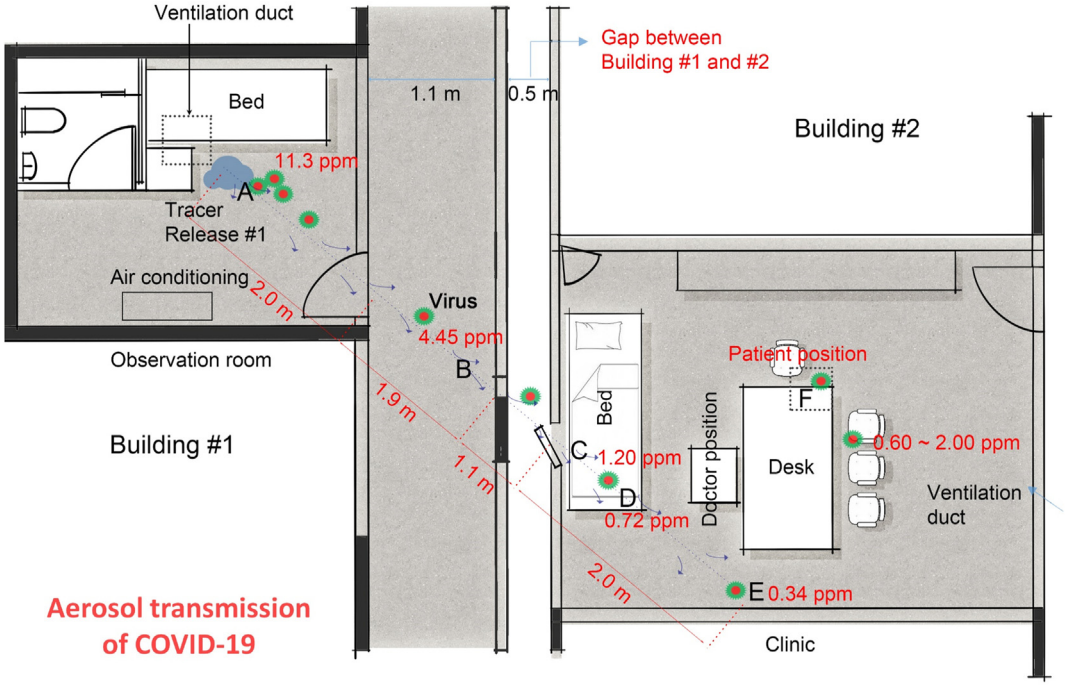

Fig. 2. Layout of the buildings where the delta COVID-19 outbreak occurred in Guangzhou in May 2021 and the tracer gas investigation illustration. The letters A, B, C, D, E, and F represent different locations in two buildings. Alcohol was used as a tracer gas and a flame ionization detector (FID) sensor was the detecting instrument.

inadequate attention with much fewer actions. To better confront the evolving pandemic, efforts and resources need to be re-allocated to study aerosol transmission and to investigate engineering solutions to defeat the pandemic. These efforts are not only useful for a current pandemic but could also be invaluable in humans' fight against future insults.

7. COVID-19 screening strategy

7.1. RT-PCR protocol

People get infected when inhaling short- or long-range SARS-CoV-2 aerosol. As of this writing, the primary strategy for mass screening of COVID-19 is to utilize RT-PCR together with pooled throat swab samples (e.g., in China, usually 10 samples are mixed for one test). There are some limitations of this strategy. There is a long waiting line for the sample collection, with a possibility of transmitting the disease to nearby people in the line. The advantage of using throat swabs is that the samples from a group of people can be pooled together for group analysis similar to airport security screening. The collection of the swab sample is fast, but can cause some discomfort to people. For analysis of SARS-CoV-2, RT-PCR as a gold standard is generally employed worldwide. However, the major problem is that sometimes COVID-19 patients can have false-negative PCR test results, thus presenting a significant infection control challenge. Accordingly, a new and rapid method must be developed to supplement the current RT-PCR test to avoid false negatives. Exhaled breath condensate was previously used to screen influenza infection by integrating silicon nanowire sensors [51]. As discussed above, COVID-19 patients were shown to exhale millions of SARS-CoV-2 particles per hour in the early disease stage [19]. The use of exhaled breath condensate together with RT-PCR tests could offer an alternative for COVID-19 screening. The advantage is that people do not have to wait for the throat swabs to be taken by the personnel. The subjects themselves can take an exhaled breath sample collection through devices made widely available, and simultaneously the procedure can reduce the risks of cross-infection by cutting short the waiting line. In addition, exhaled breath condensate collection is generally more comfortable than taking throat or nose swabs [78]. Meanwhile, exhaled breath condensate represents a different sample coming from the lower part of the lung, which could provide additional information about infections. Of course, different breath sampling protocol might collect different size range particles, which could impact the results. Besides, LAMP, as mentioned in previous sections, has lower detection limits for SARS-CoV-2 [47], and a combination of these two methods would offer a promising alternative for mass screening of COVID-19 with higher sensitivity.

7.2. Breath-borne VOC protocol

Recently, breath-borne VOC has been utilized to screen subjects for COVID-19 indirectly [79–82]. Chen et al. [32] first reported breath-borne VOC biomarkers for COVID-19. Many studies have demonstrated the promise of using breath-borne VOC for rapid screening of COVID-19 [81, 83,84]. Chen et al. [79] found elevated acetic acid and propanol levels for COVID-19, while acetone levels decreased compared to the healthy control. On the other hand, increased acetone level was observed for non-COVID-19 respiratory infections. Chen et al. [32] have found that twelve key VOC species can be used as a fingerprint of COVID-19 compared to healthy people and other upper respiratory infections. In addition, other methods have also been developed to screen COVID-19 using exhaled breath such as proton-transfer-reaction mass spectrometry (PTR-MS), gas chromatography-mass spectrometry (GC-MS), and nanosensor [81–83], as well as the use of sniff dogs [85]. For example, Shan et al. (2020) used non-VOC-species-specific sensor arrays to screen COVID-19. They were able to differentiate between COVID-19 and healthy subjects by coupling machine learning and their eight VOC signals. Using PTR-MS, COVID-19 acute respiratory distress syndrome (ARDS) and non-COVID-19 ARDS patients were also successfully differentiated by breath VOC profiles (four VOC species) [81]. It should be stressed that breath-borne VOC diagnostics is also valuable for other respiratory infections and diseases even after the pandemic [32]. Humans have many receptors for environmental contaminants, and for most of the time, unfortunately, the sensing goes unnoticed. For example, humans have an endotoxin receptor—toll-like receptor 4 (TRL4), and the bindings trigger many biological events until the signals have been translated into inflammation biomarkers such as interleukin-6 (IL-6),

tumor-necrosis factor-α (TNF-α), etc. [86]. During this process, distinctive VOCs could be released whenever the exposure occurs. Our recent work has demonstrated that when rats were exposed to airborne pollutants, including endotoxin, distinctive profiles of VOCs were found for different pollutants within a very short period [87]. In terms of COVID-19 screening by VOCs, the developed method could be impacted by background levels, medication, underlying health problems as well as possible vaccination. Together with machine learning algorithms, the patterns of VOC profiles can be well studied so that minute changes can be detected by the method. Exhaled breath samples can be treated the same as blood and urine samples, as they contain a vast amount of disease information. Future technologies should be developed to analyze biomarkers from exhaled breath so that early signs of diseases can be detected.

7.3. *Future point-of-care protocol*

Future hand-held and affordable e-nose with high accuracy for sensing breath-borne biomarkers should be developed to screen a large number of subjects for various diseases, including respiratory infections. Since the pandemic, breath-based diagnostics methods have already attracted unprecedented attention and hold a grand promise for future early disease screening and diagnosis, especially in the face of a major pandemic. At the same time, machine learning is increasingly being utilized in many areas of medical research. Breath-borne biomarkers together with machine learning could make disease diagnosis as easy and accurate as face recognition in the future [88]. This invention could also offer the opportunity for point-of-care-test (POCT) disease diagnosis even at home. Detailed analysis of breath samples could open the door for health status tracing and early disease detection. The combination offers a viable solution for future combat against the pandemic, and the relevant medical costs could also be dramatically reduced. With this being achieved, disease prevention and elimination at its embryonic stage will no longer be a scientific conception.

8. Concluding remarks

Aerosol transmission often plays a major role in infectious disease pandemics. This is true not only for COVID-19 but also for some other large-scale infectious disease outbreaks [2–4]. The use of aerosol samples can provide an early warning for the spread so that immediate control measures can be taken. Experimental, epidemiological, and environmental investigation and monitoring have demonstrated solid evidences for aerosol transmission. However, few additional actions have been taken since the worldwide recognition. Despite the substantial progress, many scientific questions remain to be answered. There is a critical need to fill the knowledge gap such that the pandemic can be better controlled with lower costs. In the reopening economy, challenges for effective control of the pandemic remain. In addition to the effort of developing various vaccines, we also need to seek technological advances for controlling the airborne transmission of COVID-19. Correspondingly, relevant sources should be allocated toward such efforts, especially in SARS-CoV-2 aerosol viability, sampling, real-time detection, and emission source control. Simultaneously, point-of-care screening methods and wearable devices for establishing breathing zone shields against the virus are also warranted. In the coming months, the world would be substantially vaccinated; however, evidence indicates that people still need other control measures in place to defeat the pandemic in response to rapid mutations of the virus. Additional engineering protocols such as aerosol control measures would minimize both human and economic costs in the pandemic era. The time left for us to further prepare for the reopening world is very limited, and actions need to be taken immediately around the globe. Scientists from different fields need to gather for the well-being of mankind to offer their help and knowledge to collectively confront such a historical challenge. This review is conducted to broadly summarize the current understanding of the aerosol transmission of COVID-19 and identify the knowledge gaps with a to-do list in protecting against the aerosol transmission of COVID-19 in a forthcoming reopening world. This review also calls for particular attention to aerosol transmission control of COVID-19 and for a request to allocate relevant resources to fill the knowledge and technology voids to better protect the world from the ongoing pandemic.

Conflicts of interest

The author has declared no conflicts of interest.

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