REVIEW

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Airborne transmission of COVID-19 virus in enclosed spaces: An overview of research methods

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Abstract

Since the outbreak of COVID-19 in December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) has spread worldwide. This study summarized the transmission mechanisms of COVID-19 and their main influencing factors, such as airflow patterns, air temperature, relative humidity, and social distancing. The transmission characteristics in existing cases are providing more and more evidence that SARS CoV-2 can be transmitted through the air. This investigation reviewed probabilistic and deterministic research methods, such as the Wells–Riley equation, the dose-response model, the Monte-Carlo model, computational fluid dynamics (CFD) with the Eulerian method, CFD with the Lagrangian method, and the experimental approach, that have been used for studying the airborne transmission mechanism. The Wells–Riley equation and dose-response model are typically used for the assessment of the average infection risk. Only in combination with the Eulerian method or the Lagrangian method can these two methods obtain the spatial distribution of airborne particles' concentration and infection risk. In contrast with the Eulerian and Lagrangian methods, the Monte-Carlo model is suitable for studying the infection risk when the behavior of individuals is highly random. Although researchers tend to use numerical methods to study the airborne transmission mechanism of COVID-19, an experimental approach could often provide stronger evidence to prove the possibility of airborne transmission than a simple numerical model. All in all, the reviewed methods are helpful in the study of the airborne transmission mechanism of COVID-19 and epidemic prevention and control.

KEYWORDS
airborne transmission, dose-response model, Eulerian method, experimental approach, Lagrangian method, Monte-Carlo model, SARS CoV-2, ventilation, Wells–Riley equation

1 | INTRODUCTION

In the past 20 years, human beings have suffered from three highly contagious coronaviruses diseases: severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and COVID-19.[1] Although the viruses that cause the three diseases are all coronaviruses, they have clear genetic differences. In contrast with the SARS and MERS viruses, the SARS-CoV-2 virus that causes COVID-19 has strong transmission characteristics, and there are no obvious symptoms in the incubation period.[2] According to the

latest real-time statistics from 1 December 2021, COVID-19 has caused a cumulative global total of 263 million confirmed cases and more than 5 million deaths. According to WHO, the COVID-19 virus (SARS-CoV-2) is transmitted through large droplets, airborne particles, and surface contact, as shown in Figure 1.

Droplet transmission refers to the direct inhalation of the virus exhaled by an infected person when a susceptible person is close to the infected person, as illustrated in Figure 1. Airborne transmission means the inhalation of small aerosol droplets exhaled by an infected person who is meters or tens of meters away. Contact transmission is the contact deposition of viruses on the surface of an object. Although WHO has suggested three possible transmission paths for SARS-CoV-2,[3] there are still many controversial theories about the airborne transmission of COVID-19. Given the growing evidence[4,5] that SARS CoV-2 could be transmitted through the air[6,7] and that the virus in small aerosol particles can survive in the air for hours, it is important to study the airborne transmission mechanism.[8]

The aerodynamic diameter of SARS-CoV-2 is approximately 120 nm (0.12 μm).[10-12] The virus cannot survive on its own; it requires a coating of proteins, such as respiratory droplets generated by human beings. The Centers for Disease Control and Prevention, USA (CDC)[13] has confirmed that SARS-CoV-2 can be transmitted by respiratory droplets produced by the coughing, sneezing, talking, or breathing of an infected person. Large respiratory droplets (>5 μm) can only remain in the air for a short time, but their horizontal travel distance is affected by the velocity of exhaled air.[14] The horizontal travel distance of most large respiratory droplets is less than 1 m.[14,15] The droplets will then deposit on the surface of an object due to gravity. Studies have shown that small aerosol droplets (<5 μm) can survive in the air for periods of 3 h to 3 days[16] and travel long distances.[16-18] According to measurements by Liu et al.,[19] the SARS-CoV-2 aerosol diameter is concentrated in the ranges of 0.25–1.0 and ≥2.5 μm. Meanwhile, Nissen et al.[20] detected viral RNA in ventilation exhaust filters that were located at least 50 m from the vent openings of a patient room. These findings provide evidence that SARS-CoV-2 may be dispersed and potentially transmitted by aerosols directly or through ventilation systems.

Many factors, such as the ventilation system, air temperature, relative humidity, and social distancing, would affect the airborne transmission of SARS CoV-2, especially in enclosed indoor spaces. Since people spend almost 90% of their time in enclosed indoor environments,[21] virus aerosols need to be rapidly discharged from indoor spaces. To effectively control the spread of COVID-19, it is essential to understand how SARS CoV-2 is transmitted in the airborne mode.

Studies of SARS CoV-2 airborne transmission have employed various means, such as probabilistic approaches (Wells–Riley equation, dose-response model, Monte-Carlo model, etc.) and deterministic solutions (Eulerian method, Lagrangian method, etc.). In the past 2 years, several review articles have been published on the airborne transmission of SARS-CoV-2 in indoor environments. For example, Elsaid et al.[22] reviewed the impact of heating, ventilation, and air conditioning (HVAC) systems on the airborne transmission

Practical implication

- The summarized transmission mechanisms of COVID-19 and their main influencing factors could help people understand the characteristics of the COVID-19 virus and take self-protection measures.
- More evidence indicated that SARS CoV-2 can be transmitted through the air.
- The reviewed probabilistic and deterministic research methods are helpful in the study of the airborne transmission mechanism of COVID-19 and epidemic prevention and control.

of SARS-CoV-2. Shen et al.[23] reviewed the proportion of infected people in different indoor environments since the outbreak of the epidemic and the use of the Wells–Riley equation to evaluate the probability of airborne infection. Noorimotlagh et al.[24] summarized the available studies on the possible airborne transmission of SARS-CoV-2. Agarwal et al.[25] reviewed control measures and sustainable preventive solutions that could be used to improve indoor air quality during the COVID-19 pandemic. However, no reviews have been published on the research methods to study the indoor airborne transmission of the COVID-19 virus. This paper seeks to fill the gap through an overview of research methods, models, and some of their recent applications.

First, this review examines the evidence for airborne transmission of COVID-19 in enclosed indoor spaces. Next, this paper presents an overview of the research methods for exploring airborne transmission. Finally, the prediction and mitigation of airborne transmission of COVID-19 in enclosed indoor spaces are discussed.

2 | EVIDENCE OF COVID-19 TRANSMISSION IN ENCLOSED INDOOR SPACES

The news media have reported numerous cases of possible COVID-19 transmission in enclosed indoor spaces, such as buildings, hospitals, airplanes, and restaurants. The cases that may involve the airborne transmission of COVID-19 mentioned in the scientific literature are summarized below.

Li et al.[26] analyzed an outbreak involving three non-associated families in Restaurant X in Guangzhou, China. People at two neighboring tables became infected with COVID-19. Figure 2 shows the simulated dispersion of fine droplets exhaled by the index patient, and the location of families B and C in the dispersion zone.

Pung et al.[27] analyzed a cluster of COVID-19 cases in Singapore. After a company conference in a confined space, six of the participants tested positive for COVID-19. Another cluster of infections consisted of six people who were infected by an asymptomatic COVID-19 patient in a karaoke bar, a confined space of less than

FIGURE 1 COVID-19 transmission mechanisms[9]
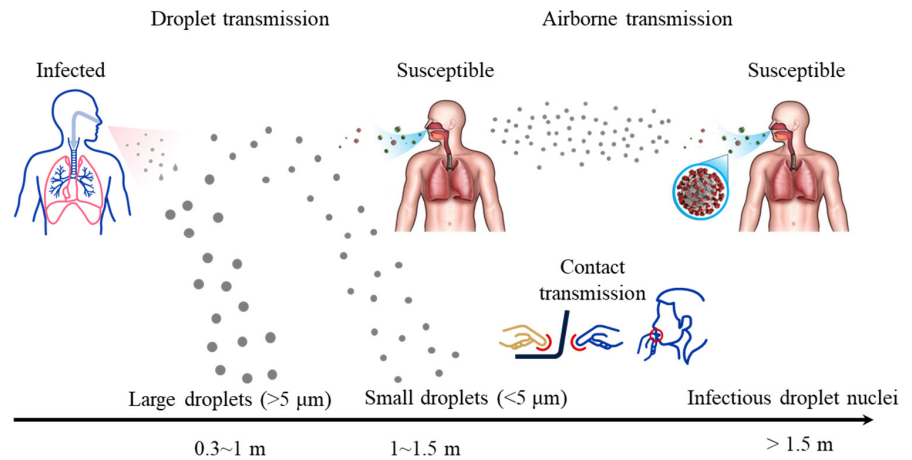
20 m^2 with many occupants and poor ventilation.[28] They suggested that the chance of COVID-19 transmission was high in a relatively confined space. Meanwhile, after a rehearsal on March 10, 2020, of the Skagit Valley Chorale, 53 of the 61 members in attendance were confirmed or strongly suspected to have contracted COVID-19, and two died.[29] They found that transmission by the aerosol route is likely; it appears unlikely that either fomite or ballistic droplet transmission could explain a substantial fraction of the cases.

Chen et al.[30] reported transmission on a flight from Singapore to Hangzhou, China, on January 24, 2020. One passenger did not wear a mask properly while he was sitting next to two COVID-19 patients inside the airplane. The authors found that COVID-19 transmission could occur in airplanes. Another transmission occurred on a flight from London to Hanoi on March 2, 2020.[31] A total of 16 people in the business-class cabin were infected by a COVID-19 patient in the same cabin. A transmission also occurred on a flight from Tel Aviv to Frankfurt on March 9, 2020.[32] Among the 102 passengers, there were 10 confirmed cases of infection. Among those cases, seven patients were part of the same tour group and had not been wearing masks. The seven patients infected at least two other people on this flight who sat within two rows of the seven patients and did not wear masks. Other cases include a flight from Boston to Hong Kong on which two flight attendants were likely infected by passengers in the same cabin[33]; a flight from Sydney to Perth on March 19, 2020, with a total of 19 confirmed cases related to the flight[34]; a flight from Milan to Seoul on March 31, 2020, with seven passengers infected[35]; and a flight from Dubai to Auckland on September 29, 2020, with four passengers infected.[36]

Shen et al.[37] examined a COVID-19 outbreak on a bus in Zhejiang province, China, in which 24 of 68 passengers were infected. They found that the airborne spread of COVID-19 was likely to have contributed to the high attack rate on the bus. Another COVID-19 outbreak event occurred during bus trips of an index patient in Hunan Province, China,[38] which suggested potential airborne transmission of COVID-19 inside the bus. Airborne infection cases were also observed on cruise ships[39] and in elevators.[40]

Table 1 summarizes the spread of COVID-19 in different settings. Although primary spread could be through large droplets in the vicinity of an infected individual, airborne transmission of COVID-19 cannot be ruled out. Transmission likely by the aerosol route was found in the considerable reviewed cases. This review examines the evidence for airborne transmission of COVID-19 in enclosed indoor spaces. Therefore, it is important to further review the influence of COVID-19 airborne transmission and the research methods for exploring airborne transmission.

3 | DOMINANT INFLUENCER OF COVID-19 TRANSMISSION

Previous studies[22-24] found that multiple parameters, such as the ventilation system,[41-43] air temperature, relative humidity, and social distancing.[43] would affect the airborne transmission of SARS CoV-2. These factors add complexity to the processes of understanding the airborne transmission mechanism of COVID-19 and assessing the infection risk. This information is essential for epidemic prevention and control. Therefore, the influence of these factors on the transmission of the SARS-CoV-2 should be addressed.

3.1 | Ventilation system

Different ventilation systems may have different effects on airborne transmission. Ventilation rate, airflow direction, and air distribution or airflow pattern are three important factors that affect the ventilation effect.[44,45] Melikov[1] demonstrated that personalized ventilation (PV) was much more effective than mixing ventilation, and a higher ventilation rate could effectively reduce airborne transmission. Mechanical ventilation was found to be far superior to natural ventilation.[46] In the area of mechanical ventilation, displacement ventilation was designed to supply clean air to the lower part of a room and remove polluted air at or near ceiling level. Since the virus sources are human beings, who are also heat sources, displacement ventilation was determined to be the most effective system for reducing the exposure risk through thermal plumes. In contrast, mixing ventilation was found to mix the indoor air evenly without providing any clean space.[45] The airflow pattern would influence the transmission path of the virus, and the air supply rate would directly affect
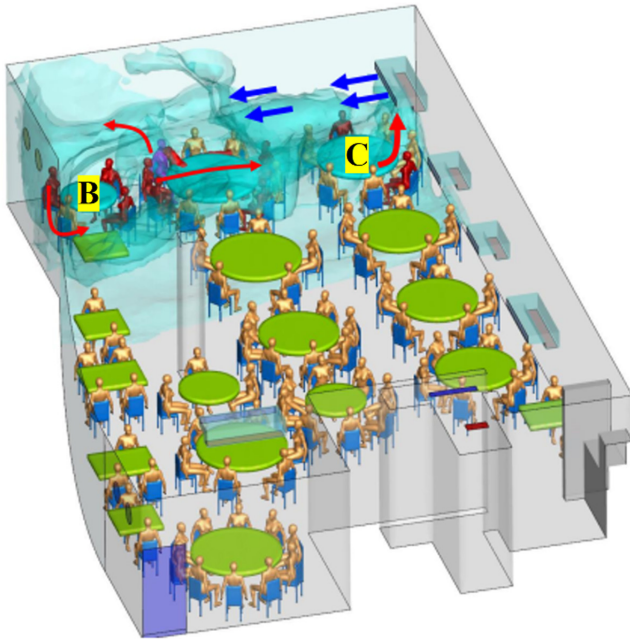
FIGURE 2 Simulated dispersion of fine droplets exhaled by index patient (magenta-blue), B and C refer to the table of family B & C[26]

the average infection risk. Since each ventilation system has its own specific requirements defined by national and international regulatory bodies based on the different ventilation objectives, WHO[44] provided a roadmap to determine the ventilation rate in different situations to deal with COVID-19.

Zemouri et al.[47] studied the effect of indoor air quality on the transmission of different infectious diseases, and their results indicated that the worse the indoor air quality was, the higher the airborne transmission probability would be. Furthermore, a study from Bisag et al.[17] demonstrated a high correlation between transmission of SARS-CoV-2 through aerosol microdroplets and poor ventilation. Bhagat et al.[45] reported that long exposure time and decreased turbulence levels in the indoor environment may be the causes of a higher infection rate indoors than outdoors. The use of a good ventilation system to improve air quality was effective in mitigating the airborne transmission of COVID-19.[17]

3.2 | Air temperature and relative humidity

Existing experimental data shows that the activity of SARS-CoV-2 decreases with an increase in temperature.[48] Chin et al.[49] found that SARS-CoV-2 can survive for 14 days at 4°C, 1 day at 37°C, and only 30 min at 56°C. Furthermore, Newell[50] reported that COVID-19 transmission efficiency was very high when the temperature ranged from 10 to 21.1°C.

A person is more susceptible to infection at low relative humidity, between 10% and 20%.[51] Virus activity does not change significantly in moderate humidity (40%–60%).[52] However, the infection risk becomes moderate when the relative humidity is high, in the range of 70%–80%.[53] As the humidity increases, the probability of infection changes

from high to moderate. In addition, experiments over the past 60 years have indicated that the activity of viral-pathogen-carrying droplets is negatively related to ambient humidity and dryness-enhanced virus spreading.[54] Moreover, the size of the particles was found to be positively related to the humidity of the air and negatively related to the air temperature. This is because of the hygroscopic growth effect[55] and evaporation vaporization. Larger particles tend to deposit on the ground due to gravity, which leads to contact transmission.

Indoor air temperature and relative humidity in offices are usually controlled at 20.3–26.7°C and 20%–60%, respectively.[56] Although these ranges are not ideal for virus survival, they do allow viruses to survive for a long time.

3.3 | Social distancing

To reduce the COVID-19 transmission through the air, the US CDC proposed 6-ft or 2-m "social distancing" between people.[57] Numerous researchers[58–63] have studied social distancing between infected and susceptible individuals as shown in Figure 3. However, this social distancing was defined with static ambient air, which is not realistic. Furthermore, indoor environments usually cannot guarantee the required safe social distance. The safety of social distancing is determined by many factors.

For example, the necessary social distance is closely related to ventilation, since the airflow can transport droplets over long distances in indoor spaces. Indoor ventilation is highly associated with the risk of respiratory infectious diseases.[64] Muthusamy et al.[65] found that without air conditioning in the room, particles spread mainly in the streamwise direction of the exhalation. However, with air conditioning, increased contaminant spread in the lateral direction was observed. The transmission path was found to be highly influenced by the relative positioning of the particle source and the ventilation supply. Sun and Zhai[66] reported that the infection risk of COVID-19 in public buses was the highest among all types of public vehicles due to the lower air distribution effectiveness, lower fresh air supply rate, and higher occupancy density. Adequate ventilation is necessary to reduce the risk of infection, such as for SARS[67] in enclosed indoor spaces.

In addition, social distancing has been defined for persons who are standing still, without considering the potential aerodynamic effects of a person's movements, such as walking. The swinging motion of legs and hands can create a complex mixing process. The wakes generated by walking can be more than 6 m long, and it can take 30–60 s for these fields to return to their original state after the movement has ceased. Studies have clearly demonstrated the potential for people's movements to influence flow fields and airborne transmission in enclosed spaces.[68] Bhattacharya et al.[69] analyzed the effects of human movement on indoor airflow patterns. They found that walking has a non-negligible effect on airflow and that the effect can continue for up to 10 s after the moving body has passed. Therefore, both the temporal and geometric distances that a healthy individual should maintain from an infected person should be based on smaller droplets under flowing air.[70]

TABLE 1 Summary of the spread of COVID-19 in different settings

Type of indoor space	Space description	Primary cases	Secondary cases	Potential transmission mechanism	Ref.
Building	Restaurant	1	9	Aerosol transmission due to poor ventilation	26
Building	Company conference	1	6	All kinds of possible transmission mechanisms	27
Building	Karaoke room	1	6	Dense population and poor ventilation	28
Building	Weekly rehearsal	1	53	Transmission likely by the aerosol route	29
Flight	Singapore – Hangzhou	15	1	Improper mask wearing and proximity to two infected individuals	30
Flight	London – Hanoi	1	15	No masks	31
Flight	Boston – Hong Kong	2	2	All kinds of possible transmission mechanisms	33
Flight	Tel Aviv – Frankfurt	7	2	Within two rows of the seven patients and no masks	32
Flight	Sydney – Perth	11	11	Aerosol transmission likely	34
Flight	Milan – Seoul	7	2	Infected in the restroom or through contact with surfaces used by infected individual	35
Flight	Dubai – Auckland	3	4	Within four rows of each other	36
Bus	100-min round trip	1	24	Airborne spread likely	37
Bus	2.5- and 1-h trips	1	10	Potential airborne transmission	38
Cruise ship	The diamond princess	1	712	Closed environment and contact	39
Elevator	–	1	1	In same elevator	40

Note: Primary cases are defined as individuals who are symptomatic or asymptomatic COVID-19 patients. Secondary cases are defined as individuals who contracted the illness through exposure to a primary case.

FIGURE 3 Relationship between exposure and the social distancing between infected and susceptible individuals[58–63]
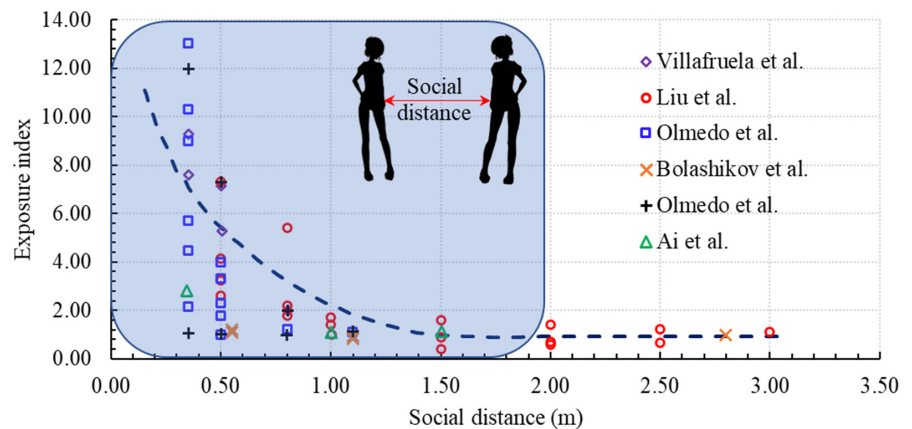
Furthermore, social distancing can be influenced by other intervention measures, such as the wearing of face masks. Deng and Chen[71] measured and simulated the mass of droplets inhaled by a susceptible manikin wearing a mask with different degrees of social distancing. They found that the distance can be reduced to 0.5 m when people wear masks. Pendar and Páscoa[72] found that wearing a face mask and bending the head during a sneeze as a protective action reduced the contamination area to one-third and three-quarters, respectively, of the area that was observed when these measures were not taken. A "safe" social distancing is highly dependent on multiple factors. Wearing masks could reduce the risk of infection and shorten the necessary social distance.

4 | STUDIES OF AIRBORNE COVID-19 TRANSMISSION IN INDOOR SPACES

Since the airborne transmission is possible in indoor spaces as reviewed above, many studies have sought to assess SARS-CoV-2 infection risk quantitatively. The research approaches used

can be classified as probabilistic methods[73] and deterministic methods.

4.1 | Probabilistic methods

4.1.1 | Wells–Riley equation

The Wells–Riley equation was first proposed by Riley et al.[74] in 1978 for studying the airborne spread of measles. The Equation (1) assumes that the virus is uniformly distributed indoors in a steady-state environment. Quanta, q, is the hypothetical infectious dose unit proposed by Wells[75] and is used to signify the strength of the infection produced by an infected individual. The number of quanta is a key parameter that varies with the type of virus. The quanta cannot be obtained in the early stage of an infectious disease outbreak and are usually backward calculated from epidemiological studies.[76] Once the quanta are known, the probability of infection risk, P, can be determined from

$$P = \frac{C}{S} = 1 - e^{-Iqpt/Q} \tag{1}$$

where C is the number of infected individuals, S the number of susceptible people, I the number of infectors, q the quanta released by an infector (h^{-1}), p the breathing rate of each susceptible person (m^3/h) with $p = 0.3$ m^3/h for a person who is sitting or engaging in light activity, t the exposure time (h), and Q the ventilation rate of fresh air (m^3/h).

Some researchers have further modified the Wells–Riley equation for other situations. For example, Zemouri et al.[47] extended the Wells–Riley equation by adding a respiratory protection factor to estimate the infection risks in dental clinics, as expressed by Equation (2). Since the epidemiologic data for SARS-CoV-1 and SARS-CoV-2 are similar,[16] the number of quanta for SARS-CoV-1 can also be used for SARS-CoV-2.

$$P = \frac{C}{S} = 1 - e^{-Iqpt(1-\eta_e)(1-\eta_r)/Q} \tag{2}$$

where η_e and η_r are the exhalation filtration efficiency and respiration filtration efficiency, respectively.

Liu et al.[77] further modified the Wells–Riley equation to evaluate the infection risk in an unsteady environment. The corresponding results can effectively guide the determination of local epidemic prevention and control measures in public spaces. To consider the actual non-uniform virus distribution in an indoor space, some researchers proposed a combination of the Wells–Riley equation with a multiple-box model[78] or a multiple-zone model,[79] experimental measurements using a tracer gas, or a computational fluid dynamics (CFD) model.[80–82] This method is helpful to fully understand the infection risk of different locations in indoor space, formulate corresponding prevention and control measures and prevent the spread of COVID-19. Note that,

experimental measurements and CFD numerical simulations can provide more accurate results than multiple-box and multiple-zone models, but they are time-consuming.

Although the Wells–Riley equation has some shortcomings, its ability to rapidly evaluate infection risk makes it an important tool during the COVID-19 epidemic.

4.1.2 | Dose-response model

The dose-response model was originally used to quantitatively evaluate the responses of animals exposed to different doses of chemical toxins, drugs, radiation, etc. In 1996, Nicas[83] was the first to use the model to assess the probability of airborne tuberculosis infection, as shown in Equation (3).

$$P = 1 - e^{-IGp\beta t/Q} \tag{3}$$

where G represents the number of airborne-transmitted virus particles released by a signal infector per unit time and β the fraction of the infectious viruses deposited in the lungs. The other parameters are the same as those in the Wells–Riley equation. In addition, the dose-response model assumes that the airborne virus particles are well-mixed under steady-state conditions. If the G times β is replaced by quanta, q, Equation (3) is the same as Equation (1). The exponential dose-response model assumes that a susceptible person would be infected when one virus particle is deposited in the lungs. Since it is difficult to assess the human infectious dose experimentally, Armstrong and Haas[84] experimented on animals and then studied the spatial distribution of infection risk through a near field-far field model[85] which was a recognized preventive exposure assessment tool.

For the Wells–Riley equation in Section 4.1.1, the quanta value was backward calculated under the assumption that all infection cases are caused by airborne transmission, and no transmission mechanism (airborne, droplet, or contact transmission) was identified as dominant. In contrast, the dose-response model could be used to explicitly consider all transmission mechanisms.[73] In addition, this review only provides the original formulas of the Wells–Riley equation and the dose-response model. Readers can find other evolution formulas from the review of these two methods.[73]

4.1.3 | Monte-Carlo model

The dispersion of an aerosol and the behavior of individuals affect their exposure to the virus. The dispersion of the aerosol is influenced mainly by the airflow, and the behavior of individuals is highly random. These factors can be addressed with the Monte-Carlo model, which uses the stochastic character of the parameters and is also known as random sampling or the statistical test method.

The Monte-Carlo model described by Vuorinen et al.[86] is used as an example to demonstrate the principles of this method as shown in Figure 4. It assesses the random movement of people and the number concentration of aerosols c (m^{-3}) = c (x, y, t) by solving the Equation (4) and diffusion Equation (5), respectively.

$$\begin{cases} N = N_0 + N_{in} + N_{out} \\ U_{i,t+1} = \begin{bmatrix} R_1 & 0 & 0 \\ 0 & R_2 & 0 \\ 0 & 0 & R_3 \end{bmatrix} U_{i,t} \ i = 1, \ldots, N \end{cases} \quad (4)$$

$$\frac{\partial c}{\partial t} = D\Delta c + S - c/\tau \quad (5)$$

where N, N_0, N_{in}, and N_{out}, represents the total indoor population, initial indoor population, number of people entering at random, and number of people leaving at random, respectively, $U_{i,t}$ and $U_{i,t+1}$ represents the walking speed with the direction of person i at t and $t + 1$ moments, respectively, R_1, R_2, R_3 represents the random variable generated by the Monte-Carlo model, t represents time (s), D the diffusion constant that would vary depending on the environment,[87] S the aerosol source term, $-c/\tau$ the sink term (ventilation or vertical surfaces, e.g., are modeled as a sink term), and τ(s) the removal timescale.

In 2020, Vuorinen et al.[86] first proposed the above Monte-Carlo model for studying the indoor exposure risk for susceptible individuals in motion sharing the same space with different numbers of individuals and different speeds of movement. Their results indicated that the developed Monte-Carlo model could quantitatively provide the duration of exposure to virus-containing aerosols. Although few studies have been published on this newly proposed method to date, it is useful in the study of virus airborne transmission in large spaces with randomly moving people, such as railway station waiting halls, airport waiting halls, shopping malls, and gymnasiums.

With the exception of an investigation by Vuorinen et al.[86], most researchers[88-90] have utilized the Monte-Carlo model to study the spread of epidemics. For example, Maltezos and Georgakopoulou[88] sought to determine the effective reproductive number in the

spread of an epidemic using the Monte-Carlo model. It should be noted that the effective reproductive number refers to the average number of secondary infections caused by a single infected person during the transmission period of the virus. This number could provide a better understanding of the fundamental mechanisms of the spread of COVID-19.

4.2 | Deterministic approaches

The probabilistic methods introduce great uncertainty to the study of airborne infectious disease transmission in buildings. Meanwhile, CFD and experimental measurements are popular deterministic tools for studying the transport of airborne particles in indoor spaces. CFD simulates particle transport by means of the Eulerian and Lagrangian models.[91,92] Experimental methods generate particles that mimic real-world virus transmission.

4.2.1 | CFD with the Eulerian model

The Eulerian model assumes that particles are a continuum and obtains whole-field information directly by solving the following scalar transport equation:

$$\frac{\partial \Phi}{\partial t} + \frac{\partial}{\partial t}(\rho \Phi V_i) = \frac{\partial}{\partial t}\left(\Gamma_\Phi \frac{\partial \Phi}{\partial x_i}\right) + S_\Phi \quad (6)$$

where Φ represents the scalar parameter; t represents the time, x_j represents the Cartesian coordinate, ρ represents the air density, V_i represents the air velocity, Γ_Φ represents the diffusion coefficient, and S_Φ represents the virus source released by the infector.

Arefi et al.[93] used the Eulerian model to study airborne particle transmission and adsorption in the human alveolus. Ho[94] investigated the impact of social distancing, ventilation mode, and face coverings on the probability of infection, and the results showed that this model was helpful for comparing and analyzing virus transmission in different scenarios. Lu et al.[95] evaluated the infection probability in hospital wards under stratum ventilation modes, and the numerical simulation results were in good agreement with the experimental results. Vuorinen et al.[86] studied the possibility of airborne transmission and the evolution of airborne particles' spatial concentration distribution over time. According to their results, a clear quantitative exposure risk with the change in time can be assessed in different public indoor environments. Srivastava et al.[96] assessed the probability of SARS-CoV-2 infection in an enclosed indoor environment using the Wells–Riley equation and evaluated the performance of an air-cleaning device. They found the Eulerian model to be a good tool for predicting the spatial distribution of airborne particles. Our review concluded that the Eulerian model, in combination with the Wells–Riley equation, is suitable for the prediction of the spatial distribution of airborne particles and assessment of infection risk.
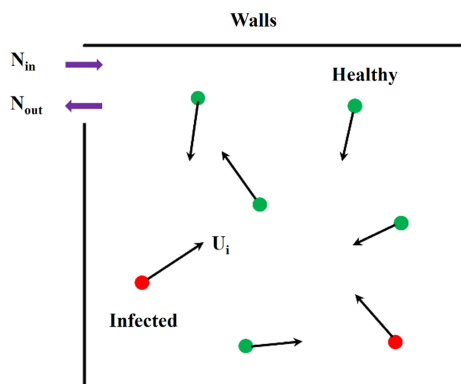

FIGURE 4 Schematic diagram of Monte-Carlo model

4.2.2 | CFD with the Lagrangian model

The Lagrangian model[97,98] determines the trajectories of individual particles using Equation (7) in accordance with Newton's law:

$$\frac{d\bar{u}_p}{\partial t} = F_D(\bar{u}_a - \bar{u}_p) + \frac{\mathbf{g}(\rho_p - \rho_a)}{\rho_p} + \bar{F}_a \qquad (7)$$

where $\bar{u}_p$ represents the particle velocity, F_D the drag force coefficient, $\bar{u}_a$ the air velocity, and $\mathbf{g}$ the gravitational acceleration; ρ_p and ρ_a are the particle density and air density, respectively; and $\bar{F}_a$ is the Brownian motion force.

Recent studies have attempted to use CFD simulations with the Lagrangian model directly to predict the risk of infection for different purposes. For example, Ren et al.[99] investigated the removal efficiency of different ventilation strategies for a prefabricated double-patient ward. Some researchers have also explored the role of the ventilation system in virus transmission in different indoor spaces with mechanical and natural ventilation.[100–102] Borro et al.[103] optimized an HVAC system by installing a local exhaust ventilation system to decrease the possibility of SARS-CoV-2 infection based on predicted infection risk results. Zhou and Ji[2] studied the effects of coughing and talking, as well as different social distances, on the infection risk in fever clinics. Feng et al.[55] investigated the impact of relative humidity and ambient wind on the effectiveness of 6-ft social distancing in decreasing the infection risk. Liu et al.[104] investigated airborne particle exposure in elevators. Li et al.[105] used the Lagrangian method to evaluate the impact of the speed, slope, and direction of an escalator on the spread of droplets. All these studies indicated that the Lagrangian model could be used to assess the risk of exposure to airborne particles.

The Eulerian and Lagrangian models are usually coupled with numerical calculations of the flow field. Hence, accurate prediction of airflow and turbulence is very important in calculating the transmission and deposition of a virus. The available CFD numerical models include direct numerical simulation (DNS), large-eddy simulation (LES), Reynolds-averaged Navier–Stokes equation simulation (RANS) with turbulence models, and detached-eddy simulation (DES). To evaluate the impact of turbulence on virus transmission, some researchers have used high-resolution LES to study indoor air turbulence,[86] turbulence generated by people's movements,[106] or the airflow generated during coughing and sneezing.[72] These researchers have sought to capture the flow characteristics and analyze the flow principle. To explore the geometric characteristics of buccal/nasal passages on virus transmission and the effects of the diffusion characteristics of salivary droplets, Fontes et al.[107] used DES to accurately capture large-scale separation flow. Their results showed that the exposure risk level caused by the diffusion characteristics of salivary droplets was highly dependent on fluid dynamics, which may vary due to human physiological factors. For the RANS method, many of the available turbulence models are suitable for different scenarios. For example, Zhang and Chen[97] adopted the modified $\overline{v^2}$-f model to improve accuracy when calculating particle deposition on a surface. Dbouk and Drikakis[108] studied the transport, diffusion, and evaporation of salivary particles caused by human coughing with and without[109] face masks, using the k-ω turbulence model.[110] Busco et al.[111] employed the realizable k-epsilon model to evaluate the effect of sneezing on transmission. Moreover, the RNG k-ε model[112] has been widely used to study transmission in indoor environments with ventilation. All the above studies have demonstrated the importance of the numerical calculation of the flow field to the Eulerian and Lagrangian models for accurate exploration of virus transmission in the region of interest.

4.2.3 | Experimental approaches

Experimental investigations of the airborne transmission mechanism have used substitutes for virus-laden particles. For example, Zhou and Ji[2] studied the particle diffusion trajectory and its spatial concentration distribution in a typical fever clinic for different situations: patient sitting and patient lying in bed. Instead of aerosol particles, they used di-ethyl-hexyl-sebacate (DEHS) droplets with diameters ranging from 0.3 to 10 μm which is a good representation of most bioaerosols. Lieber et al.[113] experimentally studied the evaporation characteristics of saliva droplets and their airborne lifetime to explore the airborne transmission of SARS-CoV-2. Meanwhile, by releasing particles produced by sandalwood combustion rather than real virus-laden particles, Kong et al.[114] evaluated the performance of a ventilation system against the exposure of healthcare workers to SARS-CoV-2 through a series of experiments. Li et al.[115] sought to analyze the airborne exposure mechanism of the virus in an aircraft cabin experimentally. They evaluated the exposure to virus-laden particles by releasing DEHS droplets in different locations in the cabin. The results of the above experiments indicated that the experimental approach of using virus-laden particle substitutes, such as DEHS droplets or particles produced by sandalwood combustion, is suitable for studying the airborne transmission mechanism of the virus.

Other types of experimental studies have also been conducted on virus transmission. For example, Li et al.[116] used an active bacterial agent to study the spatial concentration distribution and airborne transmission of a respiratory droplet aerosol. Their experimental study also explored the effects of the ventilation rate and droplet aerosol production rate on infectious disease control. Nissen et al.[20] analyzed the possibility of the airborne transmission of SARS-CoV-2 by means of various sampling methods. To study the ability of SARS-CoV-2 to transmit aerosols in hamsters, Sia et al.[4] placed a donor (COVID-19 inoculated) hamster and a healthy hamster in two adjacent stainless steel wired cages respectively as shown in Figure 5. As a result, they extracted the virus from the healthy hamsters. Richard et al.[5] performed a similar experiment using ferrets and obtained similar results. Their research showed that SARS-CoV-2 can spread through the air.

5 | DISCUSSION

Although the mentioned probabilistic and deterministic methods can help to study the airborne transmission of the virus, these methods have their unique advantages and disadvantages (Table 2).

5.1 | Probabilistic methods

5.1.1 | Wells–Riley equation

In the Wells–Riley equation, the backward-calculated quanta generation rate assumes that all infections occur through an airborne transmission mechanism. However, the actual paths of infection may also include non-direct contact and droplet transmission. Therefore, the best way to account for these two paths in the Wells–Riley equation, to make the results more accurate and persuasive, should be explored further. For example, the proportion coefficient of airborne transmission in the process of COVID-19 transmission could be determined and added to the Wells–Riley equation.

Although there have been numerous changes,[47,77] such as Equation (2), to the Wells–Riley equation to expand its scope of application, the modified Wells–Riley equation is still not suitable for all scenarios. Hence, more applicable and flexible models need to be developed.

Since the quanta generation rate used in the Wells–Riley equation is typically backward calculated from an outbreak case based on the well-mixed assumption, the effects of the outbreak case's spatial geometry, airflow pattern, and patient locations are not excluded but are implicitly included in this quanta value.[73] When that quanta generation rate is used for a new scenario, the spatial geometry and airflow pattern of the new space and the patient locations in the new space are different from those in the outbreak case, which will lead to errors. Therefore, how best to consider the effects of these factors in the Wells–Riley equation is worth further investigation.
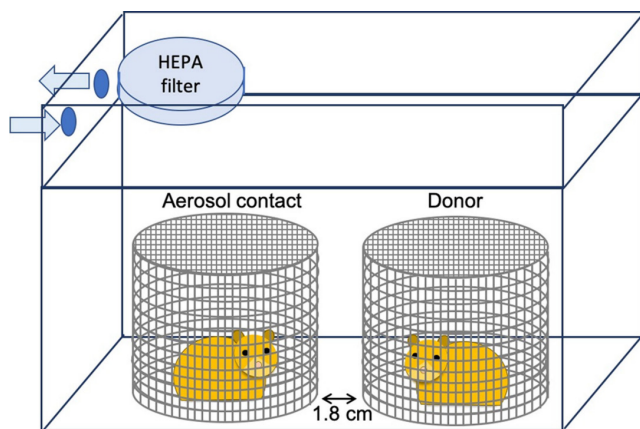

FIGURE 5 Experimental setup: the donor (COVID-19 inoculated) hamster and the healthy hamster in two adjacent stainless steel wired cages[4]

For instance, the influence factors of the outbreak case and the new space could be added to the Wells–Riley equation.

5.1.2 | Dose-response model

The quanta value used in the dose-response model is usually determined through experimental infections. However, for the animal experiments, the accuracy of interspecies extrapolation of infectivity needs to be further improved.

5.1.3 | Monte-Carlo model

The newly developed Monte-Carlo model assumes that the released aerosol is evenly mixed in a space of one cubic meter surrounding the human body and ignores the aerosol release process. The reasonableness of this assumption and whether it applies to a spatial range of any scale are worthy of further discussion. In addition, few studies have used this new proposed model to study the airborne transmission of COVID-19 to date, and therefore the accuracy of the model needs to be further verified.

5.2 | Deterministic approaches

5.2.1 | Eulerian model and Lagrangian method

Eulerian model and Lagrangian method are two usually used models under CFD methods for predicting airborne particle transmission in enclosed spaces. The Eulerian model can predict the spatial distribution of viruses throughout the whole field, but it cannot track the trajectories of individual particles. In contrast, the Lagrangian method can not only track particles but also predict the spatial distribution of the virus and track evaporating droplets.[110] However, because the original intent of the Lagrangian method was to calculate the distribution of discrete particles, the converted spatial distribution of pollutants is usually discontinuous. Therefore, most researchers prefer to use these two methods simultaneously, which is more troublesome. For example, Arefi et al.[93] used the Eulerian model to study the fine nanoparticles which are transmitted through the air, and the Lagrangian method to study the coarse nanoparticles which would be affected by Brownian motion, gravity, drag force, particle buoyancy, and so on. Although the Eulerian model is usually used to study the transmission of particles and ignores the influence of gravity, it is also possible to include the effect of gravity in the model.[117] In addition, tracking particles and predicting the spatial distribution of the virus simultaneously using the Lagrangian method would require the release of a sufficient number of particles and refinement of the mesh to minimize discontinuities in the spatial distribution of the virus.

For the simulation of a steady-state scenario, the computation time required by the Eulerian method is typically less than that for

TABLE 2 The pros and cons of different research methods

Methods	Pros	Cons
Wells–Riley equation	• Quickly determine the probability of infection risk	• Quanta cannot be obtained in the early stage of an infectious disease outbreak • Assumes that all infections occur through an airborne transmission mechanism
Dose-response model	• Determine the probability of infection risk • Explicitly consider all transmission mechanisms	• Needs rich infectious dose database to determine the infectious dose data
Monte Carlo model[86]	• Consider the highly random movement behavior of individuals when determining the probability of infection risk in large spaces	• Assumes that the released aerosol is evenly mixed in a space of one cubic meter surrounding the human body and ignores the aerosol release process
Eulerian method	• Prediction of the spatial distribution of airborne particles and assessment of infection risk • For a steady-state scenario, the computation time required by the Eulerian method is typically less than that for the Lagrangian method	• For an unsteady-state scenario, the computation time needed by the Eulerian method is typically greater than that for the Lagrangian method
Lagrangian method	• Track the trajectories of individual particles • Predict the spatial distribution of the virus and track evaporating droplets	• The converted spatial distribution of pollutants is usually discontinuous
Experimental approach	• Study the airborne transmission mechanism • Provide evidence that proves the possibility of airborne transmission	• High cost and long duration typically

the Lagrangian method. This is because the Eulerian method only needs to solve one additional scalar differential equation, while the Lagrangian method needs to track the trajectories of a large number of particles used to weaken the characteristics of the discontinuous spatial distribution of the particle concentration.[92] For simulation of an unsteady-state scenario, the computation time needed by the Eulerian method is typically greater than that for the Lagrangian method. In contrast with the steady-state scenario simulation, the Eulerian method needs a small-time step to solve the state equation and the scalar differential equation. However, the increase in calculation time when the Lagrangian method is used is mainly determined by the transient simulation time of the state equation.[92] To increase the numerical simulation speed of the state equation and scalar differential equation, future studies could adopt the fast fluid dynamics method.[118]

In Section 4.2, the Lagrange method is considered as a deterministic method. However, when the random component of turbulence is considered in the Lagrange method, this method will no longer be a complete deterministic method.

5.2.2 | Experimental approaches

Although some scholars have confirmed the possibility of airborne transmission of COVID-19 through animal experiments,[4,5] whether the results obtained from such experiments are applicable to the airborne transmission of COVID-19 between humans is worthy of further exploration. In addition, future studies could address the accuracy of interspecies extrapolation of airborne transmission possibility.

This paper only reviewed the main papers that have focused on the airborne transmission of COVID-19 in indoor environments. Up to now, almost all the papers have focused on cause-effect problems that predict the spatial distribution of indoor pollutants and the infection probability for susceptible populations on the premise that the type of HVAC system and the locations of infected persons are known. Future studies could explore effect-cause problems[119,120] that would inversely identify the locations of infected persons[121,122] from the measured known parameters.

6 | CONCLUSION

This paper summarized the possible transmission mechanisms of COVID-19 and their main influencing factors. Next, the paper reviewed the widely used probabilistic and deterministic methods for predicting the airborne transmission of SARS-CoV-2. The probabilistic methods include the Wells–Riley equation, the dose-response model, and the Monte-Carlo model, while the Eulerian method, Lagrangian method, and experimental approach are all deterministic methods.

The transmission mechanisms of SARS CoV-2 include droplet transmission, close contact transmission, and airborne transmission. There are many parameters, such as the HVAC system, air temperature, air humidity, and social distancing, that can significantly affect the airborne transmission of SARS CoV-2 in the indoor environment.

The Wells–Riley equation and the dose-response model are both based on the assumption of a well-mixed air pattern. It can only provide an average infection risk possibility, which could

cause a large error. Combining these two methods with the Eulerian method or Lagrangian method can provide more detailed information about the spatial distribution of pollutants and local infection risk.[77,96]

Both the Eulerian method and Lagrangian method can be used to assess the spatial distribution of airborne particles' concentration, but only the Lagrangian method is suitable for determining the trajectories of individual particles. The spatial distribution of the airborne particles' concentration can be used to assess the local infection risk, and the trajectories of particles are helpful in understanding the spatial transmission characteristics of the virus. Thus, both pieces of information are beneficial for epidemic prevention and control. However, the spatial distribution of the airborne particles' concentration obtained by the Lagrangian method is usually discontinuous. The best option is to use these two methods at the same time[93] for different purposes.

Compared with the Eulerian and Lagrangian methods, the Monte-Carlo model is suitable for assessing the local infection risk with the random motion of individuals. Since this model makes many assumptions, its accuracy needs to be further verified.

Although researchers tended to study the airborne transmission mechanism of COVID-19 by numerical calculation due to the high cost and long duration (typically) of experiments, an experimental approach could often provide stronger evidence to prove the possibility of airborne transmission than numerical calculations. In addition, the experimental approach can elucidate the airborne transmission mechanism and determine the possibility of airborne transmission of COVID-19.

All in all, different methods have their unique characteristics. Only by selecting appropriate methods for specific purposes can we effectively prevent epidemic diseases.

AUTHOR CONTRIBUTION

Xingwang Zhao: Investigation, methodology, visualization, data curation & analysis, writing - review & editing. **Sumei Liu**: Investigation, methodology, visualization, data curation & analysis, writing - review & editing. **Yonggao Yin**: Review. **Tengfei (Tim) Zhang**: Review. **Qingyan Chen**: Advisor, review & editing.

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The data that support the findings of this study are available from the corresponding author upon reasonable request.

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